Spontaneous Hypoglycemia as an Early Manifestation of Diabetes Mellitus

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Among the many causes of spontaneous hypoglycemia,[1] functional hyperinsulinism is the one most frequently encountered.[2] During the past several years we have been impressed by the large number of patients whose chief complaints are suggestive of functional hyperinsulinism (weakness, nervousness, tremor, hunger and sweating occurring several hours postprandially), but whose glucose tolerance tests disclose the presence of mild and usually unrecognized diabetes mellitus. The features which distinguish the oral glucose tolerance curve seen in these latter patients from the one observed in functional hyperinsulinism are shown in figure 1 and are detailed in table 1.

The purpose of this communication is to report our analyses of 110 cases of mild diabetes with secondary hypoglycemia which have been observed at University Hospital during the past six years. Our findings indicate (1) that mild untreated diabetes mellitus is frequently associated with periodic, symptomatic spontaneous hypoglycemia, and (2) that symptoms of hypoglycemia occurring three to five hours after meals represent the earliest clinical manifestation of diabetes in many cases.

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METHODS AND CRITERIA

For three days preceding the test all patients ingested a standard preparatory diet.[3] The oral glucose tolerance test was employed using 1.75 gm. of glucose per kilogram of ideal body weight, calculated from the patient's height and age. Venous blood was obtained in the fasting state and at hourly intervals for four or five hours. In many patients half-hourly samples were obtained after the second hour of the test. Blood sugar was determined in duplicate by the Nelson modification of the Somogyi method,[4] which yields "true blood sugar" values.

The criteria employed for the interpretation of the glucose tolerance test were those previously reported from this clinic.[5] Using the standard preparatory diet and the Nelson-Somogyi method on venous blood, we regard the combination of a one-hour value of 160 mg. per 100 cc. or above, plus a two-hour value of 120 mg. per 100 cc. or above, as diagnostic of the existence of the diabetic state. The following three indices were used therefore in classifying glucose tolerance curves which were diagnostic of diabetes mellitus and which also demonstrated secondary hypoglycemia:

(1) a one-hour blood sugar level of 160 mg. per 100 cc. or above;

(2) a two-hour blood sugar value of 120 mg. per 100 cc. or above;

(3) a blood sugar value of 50 mg. per 100 cc. or less thereafter.

All patients included in this study were ambulatory either as out-patients or as in-patients. None exhibited clinical or laboratory evidence of impaired hepatic function.

RESULTS

During the six-year period of observation a total of 110 patients had glucose tolerance tests which were clearly diagnostic of diabetes mellitus and which also exhibited a steep secondary hypoglycemic phase. Seventy-

TABLE 1

Functional Hyperinsulinism	Mild Diabetes with Secondary Hypoglycemia
1. Normal level of fasting blood sugar.	1. Normal or slightly elevated level of fasting blood sugar.
2. Peak venous blood sugar value *not exceeding* 140 mg. per 100 cc. ("true blood sugar").	2. Peak venous blood sugar concentration *exceeding* 160 mg. per 100 cc.
3. *Return of blood sugar to normal fasting range by the second hour.*	3. Plateau-type curve with *persistence of hyperglycemia beyond the second hour.*
4. Fall to hypoglycemic levels, usually with symptoms, between the *second and fourth hours;* followed by compensatory rise of blood sugar.	4. Fall to hypoglycemic levels, usually with symptoms, between the *third and fifth hours;* followed by compensatory rise of blood sugar.

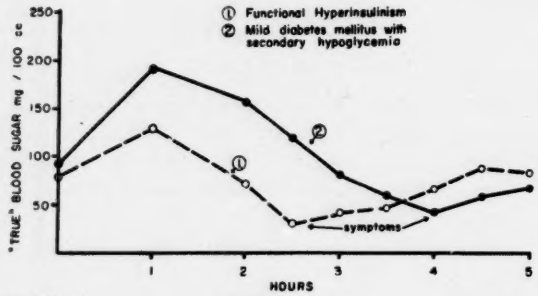

FIGURE 1

six of these patients (69 per cent) had come to the hospital seeking an explanation for complaints referable to hypoglycemia. The lowest blood sugar values attained during the glucose tolerance test were between 25 and 50 mg. per 100 cc. (mean of 42 mg. per 100 cc.) and always appeared between the third and the fifth hours (mode at four hours).

Of the 110 patients there were 70 males and 40 females. Their ages ranged from 19 to 80 years, with a mean of 48 years. Obesity exceeding 20 per cent of ideal body weight was present in 37 patients (34 per cent).

Table 2 shows a group of interesting clinical correlations. Seventy-six patients, or 69 per cent of the 110 patients with "chemical" hypoglycemia, actually had had symptoms of hypoglycemia. In this group, postprandial hypoglycemic symptoms were the chief complaints of 67 patients (61 per cent) and were secondary complaints of 9 more (8 per cent). In most of these instances the glucose tolerance test had been performed to document a presumptive clinical diagnosis of functional hyperinsulinism. Of the 34 patients (31 per cent) who did not have symptoms of hypoglycemia, the glucose tolerance test had been performed in 28 because of suspected diabetes.

TABLE 2
Clinical correlations in 110 diabetics with secondary hypoglycemia

Clinical data	No. of patients	Per Cent total
Hypoglycemic symptoms	76	69
Chief complaint	67	61
Subsidiary complaint	9	8
Known familial diabetes	48	44
Glycosuria in patient	8	7
Glycosuria in relative	1	1
Large baby in family	3	3
Symptomatic hypoglycemia and positive or probable diabetic heritage	40	36

Fifty-seven individuals, or 52 per cent of the total series, yielded definite or presumptive evidence of familial diabetes, or had shown glycosuria in the past. Forty-eight of them (44 per cent) had a known family history of diabetes. In eight persons glycosuria had been found on previous examinations, and one patient's sister had recently developed glycosuria. In addition to these 57 patients, 2 others had children whose birth weights were 10 lb. or more, and in another patient two siblings had weighed 10 lb. at birth. In only two patients had a diagnosis of diabetes mellitus been made previously, while three others had been told they had "a tendency to diabetes."

The combination of symptoms of hypoglycemia and a definite or probable diabetic heritage was found in 40 patients, or 36 per cent of the total number.

The mildness of the diabetic state when associated with secondary hypoglycemia is emphasized by the levels of the fasting blood sugar in these patients. Table 3 indicates that the level of the fasting blood sugar was below 90 mg. per 100 cc. in 83 individuals and between 90 and 100 in 19 more. Thus, 102 patients (93 per cent) had fasting blood sugar values below the upper limit of normal. In only eight individuals

TABLE 3
Fasting blood sugar values in 110 mild diabetics with secondary hypoglycemia

Blood Sugar Value (mg. per 100 cc.)	No. of patients	Per Cent total
Below 90	83	76
90 - 100	19	17
100 - 110 *	6	5
110 - 120	2	2

* Upper limit of normal = 100 mg. per 100 cc.

(7 per cent) was the value above normal, and in these it was only mildly elevated.

When glucose tolerance tests were performed on patients whose fasting blood sugar levels were in themselves diagnostic of diabetes mellitus—namely, values of 130 mg. per 100 cc. or higher—secondary hypoglycemia did not occur.

DISCUSSION

Our experience during the past six years indicates that symptomatic secondary hypoglycemia may be the earliest clinical manifestation of the existence of the diabetic state. It also points up the facts that this manifestation is frequent; that four- or five-hour tolerance tests are required to disclose it; and that the demonstration of spontaneous hypoglycemia does not rule out diabetes mellitus.

This type of hypoglycemia has been observed before, but its occurrence has been considered rare and its relationship to diabetes mellitus rather vague. When Harris first described "dysinsulinism" in 1924,[6] he presented a glucose tolerance curve showing initial hyperglycemia followed by late hypoglycemia, and he raised the possibility that the patient might be "potentially diabetic." In their review of spontaneous hypoglycemia, Skillern and Rynearson report two similar cases and draw the same conclusion.[7] Allen[8] appears to have been the first to emphasize the frequent association of symptomatic hypoglycemia and diabetes. He, too, considers the hypoglycemia to be part of a "prodromal stage" *preceding* the onset of diabetes. More recently the existence of diabetes mellitus in such cases has been overlooked, and an erroneous diagnosis of functional hyperinsulinism has been applied to them.[9, 10]

The modus operandi of this type of spontaneous hypoglycemia is not known. We postulate (1) that an early defect in diabetes mellitus consists of a diminution in the speed of mobilization of insulin in response to the stimulus of a rising blood sugar level; (2) that in this phase of diabetes the *capacity* to produce insulin remains almost normal; and (3) that the initial hyperglycemia, resulting from the lag in insulin secretion, finally affords a supernormal stimulus to the islets of Langerhans. The latter then discharge an amount of insulin sufficient to produce transient hypoglycemia. As injury to the secretory *capacity* of the islets progresses, as indicated by a rising level of the fasting blood sugar, the hypoglycemic element of early diabetes disappears. Several of our patients have progressed from the early phase (associated with hypoglycemia) to the stage of obvious diabetes with persistent fasting hyperglycemia. More difficult to prove but nevertheless impressive to the clinician are the large numbers of patients with frank diabetes who give a retrospective history of hypoglycemic symptoms which preceded the discovery of glycosuria.

In keeping with current emphasis upon the discovery and control of early, mild diabetes, it is particularly important that the type of glucose tolerance curve which exhibits early hyperglycemia and late hypoglycemia be recognized as diagnostic of early diabetes mellitus. It is not a variant of functional hyperinsulinism as has been claimed.[9, 10]

Routine diabetic management effectively controls the hypoglycemic manifestations. Treatment usually consists of reduction of caloric and carbohydrate intake in obese patients and simple restriction of carbohydrate intake in patients of normal weight. Restriction of carbohydrate to 150 gm. is usually sufficient, but very occasionally a patient with exceptionally severe symptoms may note no relief until the intake of carbohydrate is reduced to below 100 gm. In a few patients of normal weight, 10 or 15 units of depot insulin daily may be necessary in addition to the limitation of carbohydrate.

SUMMARY

During the past six years 110 patients have been observed whose glucose tolerance tests were characterized by (1) a normal or slightly elevated fasting blood sugar, (2) hyperglycemia which is prolonged for the first two hours or more, and (3) a sudden fall to hypoglycemic levels between the third and fifth hours. A possible modus operandi is suggested.

Sixty-nine per cent of these patients had complained of postprandial hypoglycemic symptoms. Forty-four per cent of them had a definite family history of diabetes mellitus. Thirty-six per cent of the group presented the combination of symptomatic hypoglycemia and a diabetic background.

CONCLUSIONS

Symptomatic spontaneous hypoglycemia may be one of the earliest clinical manifestations of the existence of diabetes mellitus. The level of the fasting blood sugar is usually normal, and a glucose tolerance test is required to make the diagnosis of diabetes.

The stimulative type of hypoglycemia associated with mild diabetes should be ranked as one of the most common forms of spontaneous hypoglycemia, since it is superseded only by functional hyperinsulinism with respect to frequent occurrence. The possibility of dia-

betes must be considered in any patient presenting symptoms of postprandial hypoglycemia. This possibility is greatly strengthened if the patient has a family history of diabetes.

The findings described are diagnostic of diabetes mellitus with secondary hypoglycemia and should not be confused with functional hyperinsulinism, a condition in which hyperglycemia does not occur.

SUMMARIO IN INTERLINGUA

Hypoglycemia Spontanee Como Manifestation Precoce de Diabete Mellite

Durante le passate sex annos, 110 patientes ha essite observate in qui le tests del toleration de glucosa esseva characterisate per (1) un normal o levemente elevate nivello de sucro sanguinee in stato jejun, (2) hyperglycemia que es prolongate pro le prime duo horas o plus, e (3) un subite reduction usque a nivellos hypoglycemic inter le tertie e le quinte hora. Un possibile modus operandi es suggerite.

Sexanta-nove pro cento de iste patientes se habeva plangite de postprandial symptomas hypoglycemic. Quaranta-quatro pro cento de illes habeva un definite historia familial de diabete mellite. Trenta-sex pro cento presentava le combination de hypoglycemia symptomatic e un fundo diabetic.

Spontanee hypoglycemia symptomatic es possibilemente un del prime manifestationes del existentia de diabete mellite. Usualmente le nivello del sucro sanguinee in stato jejun es normal, e un test del toleration de glucosa es requirite pro establir le diagnose de diabete.

Le typo stimulative de hypoglycemia associate con leve grados de diabete debe esser considerate como un del plus commun formas de hypoglycemia spontanee. Illo es excedite in frequentia solmente per hyperinsulinismo functional. Le possibilitate de diabete debe esser prendite in consideration in omne patiente qui presenta symptomas de hypoglycemia postprandial. Iste possibilitate es grandemente reinfortiate si le patiente ha un historia familial de diabete.

Le constatationes describite es diagnostic pro diabete mellite con hypoglycemia secundari e non deberea esser confundite con hyperinsulinismo functional que es un condition sin occurrentia de hyperglycemia.

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DISCUSSION

DAVID S. TRAUB, M.D., (*Louisville, Kentucky*): I want to compliment Dr. Seltzer on his interesting paper. I should like to ask him if he has followed some of the cases that he has classified as ordinary spontaneous hypoglycemia with repeated glucose tolerance tests over a period of years, and if so, as I have observed in a few instances, haven't some of those deteriorated into frank diabetes?

LEON S. SMELO, M.D., (*Birmingham, Alabama*): The problem presented by Dr. Seltzer is: What is diabetes and how is it diagnosed? The authors consider blood sugars during the initial two or three hours in excess of ADA standards to constitute a manifestation of early diabetes mellitus, notwithstanding the later exhibition of hypoglycemia in the same tolerance curve. We would raise the question: "Is not the rapid fall in blood sugar to subnormal levels a strong argument in itself against the diagnosis of diabetes?"

Since 1942 Dr. Seale Harris, with whom I formerly was associated, and I have studied many patients suspected of spontaneous hypoglycemia with six-hour glucose tolerance tests. While Drs. Seltzer and Fajans have used venous blood analyses, Drs. Harris and I have done only capillary blood sugars. With the latter procedure, we have frequently observed patients who had an elevated one- or two-hour blood sugar which dropped to a normal or hypoglycemic level by the third, fourth, or later hour. In substance these patients showed blood sugar curves corresponding to those presented by Drs. Seltzer and Fajans.

We have followed for years many of these individuals. On a very rough basis I think it safe to say that we could demonstrate no greater development of overt diabetes in these patients than would be expected in the general population among persons of equivalent age, weight, and familial background. We infer therefore that such a tolerance curve is not evidence of early diabetes.

We have taken a fair number of persons with the type of tolerance curve under discussion and have attempted to clarify their diabetic status by forced feeding of carbohydrate. After the initial tolerance test, four or five hundred grams of carbohydrate per day were administered for a week or so and then the tolerance test was repeated. We felt that this regime would intensify an early or latent diabetes so that the second curve would show more marked deviation from standard normal figures than the first. To date, all second tolerance curves have revealed a shift toward or to normal. This observation is further substantiated by the fact that in the follow-up of these cases and of similar cases for as long as a dozen years, no clinical diabetes has become manifest. Thus, our observations contravene the view that a tolerance curve with initial hyperglycemia followed by hypoglycemia constitutes a manifestation of early diabetes.

RANDALL G. SPRAGUE, M.D., (*Rochester, Minnesota*): In the course of his presentation Dr. Seltzer referred several times to the development of hypoglycemia three or more hours after the administration of glucose as "functional hyperinsulinism." I would like to ask if he believes that the observed hypoglycemia is actually due to an excessive secretion of insulin. If so, this would be a most interesting phenomenon in individuals with diabetes. My own feeling is that some such term as "functional hypoglycemia" should be used until we have positive evidence that the hypoglycemia is due to oversecretion of insulin.

ARTHUR A. HEROLD, SR., M.D., (*Shreveport, Louisiana*): At the risk of being repetitious, I would like to pose a question applicable to both Dr. Wilkerson's paper and the last paper which we enjoyed, both of which are excellent presentations, in my opinion.

I would like to know how they feel about giving indiscriminate glucose tolerance tests to every one about whom there is any doubt of diabetes, especially those that have no symptoms or evidence by either fasting or postprandial blood sugars.

I am wondering if a patient who had a slight predisposition to the disease could not have it precipitated by the large doses of glucose which are given in these cases.

I have in mind at least one case, and I think I know several, in which diabetes did not develop until after the glucose tolerance test was given. I realize, of course, it is necessary in many cases. I think to take a whole group of people and give every one a glucose tolerance test is an error.

HOLBROOKE S. SELTZER, M.D., (*Ann Arbor, Michigan*): May I first thank all the discussers for their comments. Dr. Traub, I am not aware of any evidence indicating that functional hyperinsulinism is a prediabetic condition. Although we have not specifically investigated this point, we have not been impressed by any untoward incidence in our own cases.

In support of Dr. Smelo's opening remark, the type of glucose tolerance curve we have presented was first described by Dr. Seale Harris in his original paper on spontaneous hypoglycemia in 1924. However, although he labeled the patient who showed such a curve a "potential diabetic," the true correlation between diabetes and hypoglycemia was not brought out.

The question: "What constitutes a diagnosis of diabetes?" is especially pertinent when we are dealing with the early and mild stage of the disease. Our criteria for the diagnosis of diabetes consist of a one-hour value of 160 mg. per 100 cc. or above, *plus* a two-hour value of 120 mg. per 100 cc. or above, using the "true blood sugar" method. These limits are actually slightly higher than those proposed by Mosenthal.

In this connection, one sometimes hears mild but unequivocal diabetes mellitus described as "laboratory diabetes," which implies some sort of distinction from "clinical diabetes" characterized by glycosuria and its attendant symptoms. In view of present-day emphasis on early recognition of the disease, it is surprising to meet such resistance to the concept that otherwise unexplained decreased carbohydrate tolerance, of whatever degree, is diagnostic of bona fide diabetes. Moreover, when so-called "laboratory diabetes" goes untreated there tends to be a progressive rise in the glucose tolerance curve, although the rate of this deterioration is not predictable in the individual patient.

Regarding those patients in whom the second glucose tolerance test was better than the first one, I wonder if they had received standard dietary preparation prior to the first test? We sometimes see a mild diabetic whose random fasting blood sugar level is 110 mg. per 100 cc. or thereabouts. After consuming 300 gm. of carbohydate daily for three days his glucose tolerance test is diagnostic of diabetes, but the fasting blood sugar has

fallen to 80 or 90 mg. per 100 cc. Presumably the glucose tolerance curve would have been even more abnormal had it been done without first stimulating the islets to their maximal insulin-secreting capacity with the high carbohydrate intake.

Dr. Sprague very rightly challenges our use of the term "functional hyperinsulinism" as a synonym for the more general term "functional hypoglycemia" before actual proof exists that increased insulin secretion is the cause of the hypoglycemia. Dr. Vallance-Owen's recent development of a sensitive method for determining plasma insulin concentrations should finally enable this crucial point to be settled. In the meantime, abundant indirect evidence has led Dr. Conn to conclude that the underlying mechanism in "functional hyperinsulinism" is excessive insulogenesis in response to a normal postprandial rise in blood sugar concentration.

Finally, in reply to Dr. Herold, we would not anticipate any danger of precipitating diabetes by administering 100 gm. of glucose to a patient with normal carbohydrate tolerance. The patients you describe probably had pre-existing mild diabetes which did not become clinically apparent until after the glucose tolerance test was performed.

Enzymatic and Metabolic Adaptations in Animals

HORMONES AS ACTIVATORS AND INHIBITORS. No hormones have as yet been recognized to be themselves enzymes or coenzymes, nor to exert catalytic effects in physiologically occurring chemical reactions. The rarity of physiologically occurring activators or inhibitors of enzyme systems already referred to does not support the view that the hormones, which must be present in most tissue extracts, act as simple activators or inhibitors of the enzyme reactions which have been studied.

IDENTIFICATION OF THE ENZYME REACTIONS AFFECTED. The physiological change resulting from hormone administration in vivo usually represents the product of a number of biochemical reactions, any one of which might be altered by the hormone. That efforts to demonstrate hormone effects on known enzyme reactions have failed may therefore mean that the correct reactions have not yet been tested. But this possibility becomes increasingly unlikely as more and more reactions are recognized and studied. If hormones should act on enzyme systems directly, it would now appear that the reactions affected would be those, like specific protein syntheses, which are of a different general type from the reactions studied up to the present.

EFFECTIVE CONCENTRATION OF HORMONES. The concentrations of hormones required to produce measurable effects in vitro are generally considerably higher than those normally found to be effective in vivo. As an example, the oxidative phosphorylation of liver mitochondria was inhibited by 10^{-4} M thyroxine, and the usual decline of succinoxidase activity in an in vitro system was prevented by 1 to 5 x 10^{-5} M thyroxine. The physiological concentration of thyroxine in the blood is estimated to be around 10^{-8} M, based on protein-bound iodine. In order for these direct effects of thyroxine on enzyme activity to occur in vivo, the cells would have to concentrate the hormone by several orders of magnitude.

SELECTIVE ACTION OF HORMONES ON ENZYME SYSTEMS. The physiological significance of the effects on cell-free enzyme systems produced by hormones can be assessed only by comparison of these effects with the effects of the same hormones observed in vivo after the administration of the hormones to the animals. The in vivo effects of hormones on enzyme systems are characterized by a high degree of specificity. Thus a given hormone may affect differently a given enzyme in different tissues, or in the same tissue of animals in different metabolic states. A given hormone may affect different enzyme systems in the same tissue to different degrees or in opposite directions. Such a high degree of selectivity is seldom manifested by hormones acting on cell-free enzyme systems.

From the book by W. E. Knox, V. H. Auerbach, and E. C. C. Lin, in *Physiol. Rev.* 36:164-254, 1956.

Primary Aldosteronism and Its Relationship to Diabetes Mellitus

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Primary aldosteronism now is a recognized entity, and aldosterone-producing tumors can be clinically diagnosed. Aldosterone is 20 to 30 times as effective as desoxycorticosterone in maintaining electrolyte balance and well-being in patients with Addison's disease, and approximately one-third as effective as cortisone in causing deposition of hepatic glycogen in adrenalectomized animals.

Twelve cases of primary aldosteronism have been reported in the literature,[1-5] excluding the three cases summarized here. Of the total of 15 patients, 11 have been cured — 10 by removal of adrenocortical adenoma and one by bilateral adrenalectomy. Three of the remaining four cases were diagnosed only at autopsy when adrenal adenoma was found.[3] Finally, one patient had adrenocortical carcinoma that produced solely mineralocorticoid effects, presumably due to excessive aldosterone secretion.[6] A diagnosis of primary aldosteronism has been proved by demonstration of a tumor in some cases previously diagnosed as "potassium-losing nephritis."[1, 5]

Since aldosterone has a cortisone-like effect, it is probable that some patients having severe or long-standing aldosteronism will have diabetes. Diabetes has not been a prominent feature among the few known cases; however, our own limited experience with three cases suggests that diabetic tendency in aldosteronism may be shown only by a glucose tolerance test. In the cases reported heretofore, the absence of diabetes has been definitely established by a normal glucose tolerance test in only one case, that reported by Conn.[1] In the case reported by Mader and Iseri[2] the fasting blood sugar level was 76 mg. per 100 ml.

We have observed three patients having primary aldosteronism; full reports of these cases will be published soon.[7] All three patients had proved adrenocortical tumors associated with an excess of aldosterone in the urine which was identified as the diacetate by fractionation of chloroform extracts of urine, using chromatography and ultraviolet spectrometric analysis. One of four fractions showed a sodium-retaining power eleven times that of desoxycorticosterone, and a homogeneous material prepared from this fraction had an absorption spectrum and a bioassay identical to those of aldosterone. Details of this fractionation method are to be published elsewhere. Each of the three patients had some evidence of abnormal carbohydrate metabolism.

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SUMMARIES OF CASES

The first patient, a 44-year-old man, for several years had had attacks of generalized weakness lasting one to two days. He had had arterial hypertension since the age of nineteen years. The blood pressure was 200/128 mm. Hg. There was questionable early papilledema, but there was no peripheral edema.

Outstanding laboratory features were high serum sodium levels of 140 to 148 mEq., depressed serum potassium levels of 2.6 to 3.0 mEq., alkalosis with CO_2-combining powers of 32 to 36 mEq. per liter, and normal levels of serum chloride. An oral glucose tolerance test yielded the following results: fasting, 107 mg.; one-half hour, 145 mg.; one hour, 261 mg.; two hours, 222 mg.; three hours, 171 mg.; and four hours, 80 mg. per 100 ml. There was no glycosuria. Repeated urinalyses never showed an acid urine. An Addis test showed that there was inability to concentrate urine and there was some excess of cells. Urinary 11-oxysteroid and 17-ketosteroid titers were normal. The electrocardiogram was compatible with hypokalemia. Retroperitoneal oxygen insufflation demonstrated an adrenal tumor; on removal, it weighed 25 gm.

On the fourteenth postoperative day the serum sodium level was 133 mEq., CO_2-combining power 26 mEq., serum chloride level 96 mEq. per liter; and the serum potassium level was abnormally high, 5.5 mEq. per liter, and remained so for some months. The blood pressure was 140/84 mm. Hg. The glucose tolerance test after three days of a high-carbohydrate diet yielded the following results: fasting, 81 mg.; one-half hour, 111 mg.; one hour, 104 mg.; two hours, 148 mg.; three hours, 119 mg.; four hours, 78 mg. per 100 ml.

Six and one-half months after surgery the glucose tolerance was as follows: fasting, 86 mg.; one hour,

152 mg.; four hours, 45 mg. per 100 ml. The serum potassium level was 5.3 mEq. and the CO_2-combining power was 22.3 mEq. per liter.

The second patient, a 63-year-old woman, was admitted to the hospital with generalized paresis. During the preceding year she had lost 25 lb., and now weighed 97 lb. The blood pressure was 170/100 mm. Hg.

Outstanding laboratory findings included: serum sodium level, 139 mEq.; serum potassium level, 1.7 mEq.; CO_2-combining power, 31.2 mEq.; serum chloride level, 90.3 mEq. per liter; fasting blood sugar values, 309 and 406 mg. per 100 ml.; and urinary corticoid and 17-ketosteroid titers, normal. There was inability to concentrate urine and the patient had polyuria. The urine never was found to be acid. An Addis test showed a specific gravity of 1.010 and a urinary volume of 1,100 ml.

The diabetes was controlled with a 1,638-calorie diet containing 177 gm. carbohydrate, 74 gm. protein, and 20 units of NPH insulin per day. The insulin requirement gradually decreased to 7 units per day.

An encapsulated adrenocortical adenoma, 1 cm. in diameter, was removed. Immediately preoperatively on a carbohydrate intake of 213 gm. and without insulin, blood sugar levels before each of three meals had been 132 mg., 182 mg., and 285 mg. per 100 ml. Thirteen days postoperatively on a carbohydrate intake of 210 gm., blood sugar levels were 103 mg. fasting and 106 mg. per 100 ml. one and one-half hours after the noon meal. Glycosuria was noted only on the first day of her admission and after intravenous administration of glucose.

Three months after operation she had gained sixteen pounds and had no further weakness; the blood pressure was 150/100 mm. Hg, and the electrolyte pattern was normal. After an unrestricted diet for three months, blood sugar levels were 158 mg. per 100 ml. three hours after eating and 132 mg. per 100 ml. four hours after eating. Oral glucose tolerance remained abnormal: fasting, 112 mg.; one-half hour, 207 mg.; one hour, 275 mg.; two hours, 428 mg.; three hours, 437 mg.; and four hours, 300 mg. per 100 ml.

The third patient, a 42-year-old woman, had had increasing spells of weakness, sometimes with unconsciousness, for two years. Blood pressure was 220/120 mm. Hg and there was no peripheral edema. The electrolyte pattern was similar to that found in the other two patients; and, as in the other patients, there were inability to concentrate urine and a tendency toward alkaline urine.

In December 1952, the oral glucose tolerance was as follows: fasting, 70 mg.; one-half hour, 127 mg.; one hour, 173 mg.; two hours, 163 mg.; three hours, 135 mg.; and four hours, 62 mg. per 100 ml. In May 1955, before the adrenal adenoma was removed, the glucose tolerance was as follows: fasting, 100 mg.; one-half hour, 160 mg.; one hour, 153 mg.; two hours, 133 mg.; three hours, 86 mg.; and four hours, 66 mg. per 100 ml.

Four and one-half months postoperatively the patient was asymptomatic, but still had some arterial hypertension.

CONCLUSIONS

On the basis of the limited experience to date, the incidence of diabetes in primary aldosteronism cannot be determined. It appears that the diabetes that does arise as a result of excess of aldosterone is of a very mild variety. In one of our three patients having primary aldosteronism, the diabetes has not disappeared completely following the removal of the tumor, yet there appears to be no family history of diabetes.

SUMMARIO IN INTERLINGUA

Aldosteronismo Primari e Su Relation a Diabete Mellite

Super le base del limitate experientias nunc disponibile, le incidentia de diabete in aldosteronismo primari non pote esser determinate. Il pare que le diabete que occurre como effecto de un excesso de aldosterona representa un levissime varietate. In un de nostre tres patientes con aldosteronismo primari, le diabete non ha disparite completemente post ablation del tumor, sed apparentemente le caso es sin historia familial de diabete.

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Natural Course and Prognosis of Juvenile Diabetes

Priscilla White, M.D., Boston*

One thousand seventy-two juvenile patients of the Joslin Clinic have now lived for more than twenty years. Since in the United States today there are some one hundred thousand individuals who also are surviving childhood diabetes, a summary of the unique experiences of these long-term cases appears to be of value. What is their present status? Why did they develop diabetes? What was the entire course of their disease? How did they grow and mature? What complications did they develop? How did they die and, finally, what can be done toward the solution of their problems?

Status. These 1,072 patients comprise 28.7 per cent of the 3,732 juvenile cases treated at the Joslin Clinic up to Aug. 1, 1955. Their present status shows that 82 per cent (879 patients) are living, 16 per cent (169 patients) have died, and 2 per cent remain untraced.

Present age and duration. These patients are, of course, no longer children. The oldest (also treated by Dr. John Williams) at fifty-six years of age has survived his diabetic adolescence, youth, middle age, and is now entering the technical old-age period. The majority (61 per cent) are now between 30 and 39 years of age, with 18 per cent between ages 20 and 29, 20 per cent between ages 40 and 49, and 1 per cent now over age 50. The duration of diabetes to Jan. 1, 1956, or to death varied from 20 to 42 years; 70 per cent survived 20 to 29 years and 30 per cent over 30 years, including 3.2 per cent over 35 years.

Achievements. Their struggle to survive and their struggle to achieve, even after the development of multiple disabilities, was amazing. A famous case of pituitary dwarfism, reported by Beck and Suter,[1] totally blind and with renal failure, earned his PH.D. degree. A total comprising 30 per cent received college education; 5 per cent did graduate work. They achieved a high socio-economic level. Their occupations compared more than favorably with the Minnesota scale[2] for urban populations for males. Those in professions, 26 per cent, exceeded the number expected in the general population, 6 per cent, by more than four times.

By age at onset and sex distribution, they are typical of all juvenile diabetics. The peak for age at onset was eleven years and the sex distribution was even. For the most part their attitude and that of their parents had been one of acceptance of the problem. The patients' cooperation in the measuring of food, performance of tests and regulation of insulin was good. Their past treatment, however, had not been uniform, since the group includes all patients registered in the clinic—those under continuous care, those seen occasionally, those seen only once in consultation, as well as those who came for terminal care. Management with respect to caloric prescription, partition of diet, type of insulin and frequency of insulin injections was varied.

Etiology. Because of the many opportunities to recheck family histories, the hereditary predisposition to diabetes was revealed in 57 per cent. The data compiled from these long-term cases again support the thesis that the transmission is through Mendelian recessive genes.[3] Thus, in spite of the advancing age of their parents, only 13 per cent had one or more diabetic parent. Although one patient could trace her diabetic ancestry for five generations, three-generation cases were exceptional. Compared with an expectation of 22 per cent diabetes[4] in their life span for the children of a single diabetic parent, only 1 per cent had offspring with diabetes. Four per cent of the girls had diabetic sisters and 5 per cent had diabetic brothers. Six per cent of the boys had diabetic brothers and 4 per cent had diabetic sisters. The prenatal maternal influence upon diabetes production[5] was not shown at the time of this study, for the number of diabetic fathers equaled the number of diabetic mothers. The peculiar age behavior of diabetes was again indicated in the family histories, 1 per cent of the cases showing it in direct descendants, 13 per cent in the parent group and 18 per cent in the grandparent group.

Natural course of diabetes. The natural course of

Presented at the Sixteenth Annual Meeting of the American Diabetes Association in Chicago on June 10, 1956.

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diabetes, recognized by those who see many of these cases,[6] is shown in its entirety in this long-term group. The onset of their symptoms occurred typically in a day, week or month. The first recognition in many was in diabetic coma. Despite this virulence of the early course, remissions of the diabetic state occurred in one-third. On occasions the remission was so marked that the standard glucose tolerance test returned to normal. Gradually the insulin requirement increased to one-half unit per pound of body weight. Intensification of the diabetic state appeared to be affected more by linear growth than by gain in weight. It was also intensified by the intercurrence of infections of the common types as well as by bouts of ketoacidosis. The requirement for insulin at the completion of growth and development (age twenty) was compared with the last recorded doses. Although as adults 75 per cent of the females and 56 per cent of the males required less insulin than before age twenty, the decrease of dose in units was slight. Insulin requirement fell 50 per cent in only 5 per cent of males but in 20 per cent of females.

Examination of the pancreatic islets in thirty-one autopsied cases, with ages between 20 and 41 years and duration of diabetes between 20 and 31 years, showed diminution in islet size, number and cellular differentiation in 93 per cent. None showed hypertrophy or hyperplasia. These changes are not reported in short-term juvenile diabetics. The clinical course of these patients along with the pancreatic assays (by Wrenshall),[7] blood assays (Bornstein),[8] the histological reports (Bell),[9] and the findings of Warren,[10] all imply that the total or near total diabetic state is eventually acquired by the juvenile patient.

Growth. The linear growth of these patients was for the most part satisfactory. The median height finally attained by the males was 68 inches and by the females 63 inches, comparable to general experience. Perhaps because they were treated in part with undernutrition in the preinsulin era, 7 per cent of the males did not attain an adult stature of 63 inches and 8 per cent of the females did not attain a height of 60 inches.

The weight after age twenty was maintained at a normal or more often a sub-normal level in nearly 90 per cent (51 per cent of the males and 45 per cent of the females were five or more pounds below weight). Only 14 per cent of females and 13 per cent of males were five or more pounds above weight for height.

Menses. Sterility. Pregnancies. Although very few American girls have not menstruated before age fourteen,[2] only 28 per cent of these patients had matured at that age. The median age for their first menses was fifteen. However, there was no evidence of hypo-ovarianism in their later life. Sterility was *no* problem. Among 473 pregnancies, including reported and observed cases, their fetal wastage was high, 40 per cent, compared with the expected of 13 per cent. Their abortion rate was two and one-half times normal and their perinatal loss was six times the normal. The reported infancy death rate was 0.4 per cent and the incidence of gross anomalies only 2 per cent (both probably below the actual figures).

The harmful influence of maternal diabetes upon fetal salvage is suggested by the contrasting figures on the perinatal losses of the wives of the diabetic males in this series. They reported the loss of 3 per cent, exactly that of the general population.

Complications. In varying degrees of intensity and frequency these 1,072 patients had developed the major complications of diabetes: coma, infections, neuritis and vascular damage. Severe ketoacidosis or coma had occurred in 52 per cent of the females, multiple attacks in 18 per cent. The incidence in the males was 39 per cent, with 12 per cent having multiple attacks.

In the order of descending frequency they had abscesses and carbuncles, pyelonephritis, tuberculosis and osteomyelitis (in an incidence of 33, 12, 4 and 0.5 per cent respectively for the females; 30, 2, 4 and 0.8 per cent respectively for the males). Neuropathy had occurred too often, in 26 per cent of the females and 20 per cent of the males. Acroneuritis was the form observed most commonly, with gastrointestinal neuropathies in second place. Such malignant neuropathies as Argyll Robertson pupils, tabetic bladders, and Charcot joints occurred infrequently, in only 0.3 per cent, 0.3 per cent and 0.5 per cent respectively.

From incidence, disability and mortality, vascular damage was by far the most important complication. At thirty-five years' duration nearly all showed lesions; 94 per cent had calcified arteries, 93 per cent retinopathy, 59 per cent neovascularization, 53 per cent hypertension, and 44 per cent had nephropathy. These lesions were not observed in the first five years of diabetes, rarely found in the first ten years, but by fifteen years, 19 per cent of those examined had retinopathy, 14 per cent calcified arteries, 7 per cent proteinuria, 4.5 per cent hypertension and 3 per cent proliferans.

The lesions were rare under age twenty but were prevalent by age thirty (63 per cent had retinopathy, 46 per cent had calcified arteries, 29 per cent had retinitis proliferans, 34 per cent had albuminuria, and 40 per cent hypertension). Although the incidence of the disabilities arising from the vascular lesions for the

TABLE 1

Age and duration of 879 juvenile diabetics surviving more than twenty years

Present age				
Years 20-29 per cent	Years 30-39 per cent	Years 40-49 per cent	Years 50-56 per cent	Total
18	61	20	1	100%

Present duration					
Years 20-24 per cent	Years 25-29 per cent	Years 30-34 per cent	Years 35-39 per cent	Years 40-42 per cent	
31	40	24	<5	<0.2	100.2%

TABLE 2

Occupations of males among 879 juvenile diabetics surviving twenty years (Minnesota Scale for Urban Populations)

	Expected per cent	Actual per cent
Professional	6	26.3
Semiprofessional	13	18.1
Clerical	29	22.7
Farmers	0.4	2.3
Semiskilled	29	16.8
Slightly skilled	13	6.9
Day labor	8	5.3

TABLE 3

Total incidence of vascular lesions by age

Age Years	Albumin per cent	Blood pressure per cent	Retinitis all types per cent	Retinitis proliferans per cent	Calcified arteries per cent
0-9	0	0	0	0	0
10-19	4.2	1.8	4.8	0	6.5
20-29	18.5	16.7	63.2	28.7	45.5
30-39	34.7	40.3	84.4	53.1	83.3
40-49	37	51.9	88.0	58.4	95.0
50+					

TABLE 4

Total incidence of vascular lesions by duration

Duration years	Albumin per cent	Blood pressure per cent	Retinitis per cent	Retinitis proliferans per cent	Calcified arteries per cent
0-4	0.8	0.5	0	0	0
5-9	1.5	1.2	2.5	0	1.7
10-14	7	4.5	19	3	14
15-19	18	15	59	18	44
20-24	41	32	82	47	73
25-29	39	44	88	46	88
30-34	44	53	93	59	94
35-39	63	70			

TABLE 5

Causes of death
169 cases (16% of 1,072)

	Number	Per cent
All causes	169	100
Diabetic coma	1	0.6
Cardio-renal-vascular	148	87.5
Arteriosclerotic Cardiac	8	4.7
Angina pectoris or Coronaries	45	26.6
Nephritis	86	50.9
Apoplexy	9	5.3
Infections	5	2.9
Tuberculosis	2	1.2
Accidents	3	1.8
Suicide	1	0.6
Murder	1	0.6
Appendicitis	2	1.2
Sepsis	1	0.6
Necrotizing papillitis	1	0.6
Hypoglycemia	1	0.6
Unknown (diabetes)	3	1.8

TABLE 6

Age and duration at death (169 cases)

Age at death				
Years 20-24 Per cent	Years 25-29 Per cent	Years 30-34 Per cent	Years 35-39 Per cent	Years 40+ Per cent
2	20	43	25	10

Duration at death				
Per cent	Per cent	Per cent	Per cent	Per cent
64	25	11	0	0

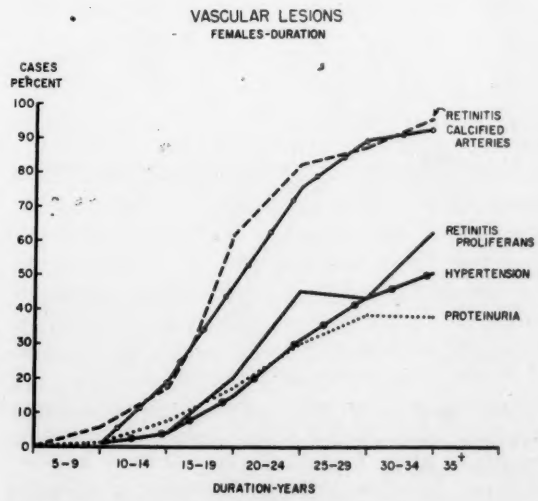

FIGURE 1

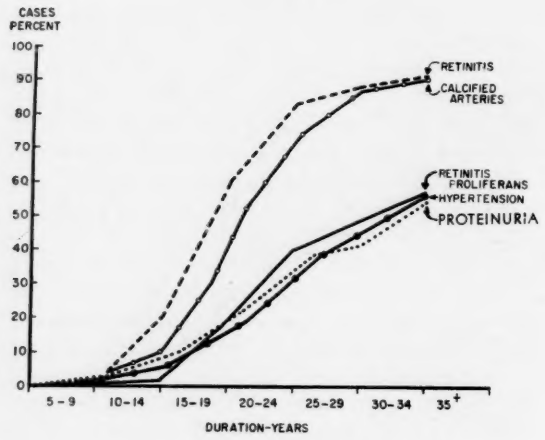

FIGURE 2

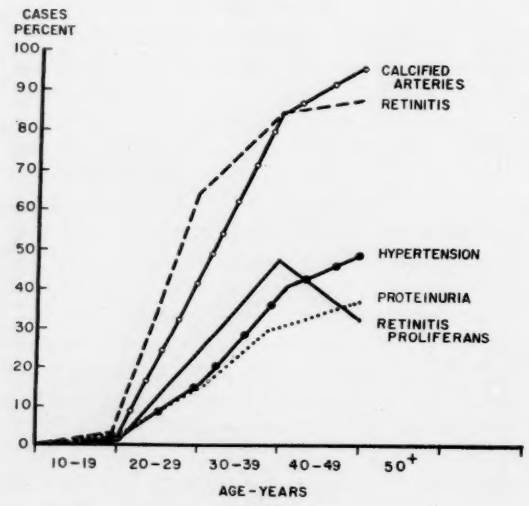

FIGURE 3

entire series of living and fatal cases is appreciable (uremia in 9 per cent, blindness in 6, myocardial infarction in 6, cerebrovascular accident in 2 and gangrene in 0.5 per cent), there is increasing evidence that certain numbers of these patients show a stationary status of their vascular lesions. This favorable course can be evaluated best in the retina.

Although it is evident from the foregoing that all of the vessels of these young patients are involved in all

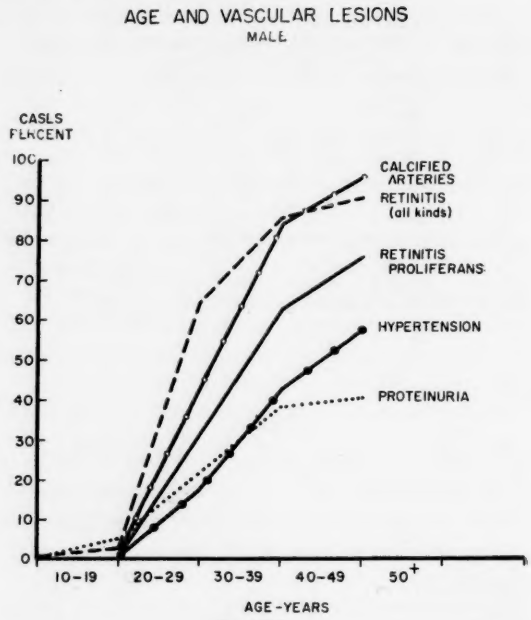

FIGURE 4

types of sclerosing processes, the significant, progressive and lethal lesions involve the arterioles, capillaries and venules. These small vessels can be observed at the microscopic level in the bulbar conjunctiva. Such examinations have been made upon this group by Ditzel[11] and have shown two types of patterns. One is characterized by the loss of venular tone and by venular dilatation. The second is characterized by increased arteriolar constriction. The changes are followed by intravascular aggregation of erythrocytes, by perivascular edema and by hyaline deposition. Long-term diabetics show these abnormal responses, and untreated and uncontrolled cases to an exaggerated degree. It is significant that these changes were also observed in children of diabetic mothers, 16 per cent in those with normal glycemia, 51 per cent in those with hyperglycemia.

Because Fanconi[12] reported 100 per cent mortality from nephropathy in juvenile diabetes before the twentieth year of the disease and because he attributed it to the low protein content of his diets, the dietary management of these patients was reviewed.

Patients were classified according to presence or absence of vascular lesions, as perfect, minimal, moderate, and severe. *Minimal* lesions included microaneurysms and/or calcified arteries; *moderate* included blotchy hemorrhages; and *severe* included proteinuria and neovascularization in the retina. The weights and prescribed diets and insulin were compared. There were

no significant differences and, in this group, vascular lesions did not appear to be iatrogenic in origin.

Unusual procedures. The most remarkable procedures experienced by this group were the removal of a pheochromocytoma, an aorta graft and a single transplantation of fetal pancreas. These two last procedures were done recently and the influence upon the diabetic state has not been revealed.

Mortality. Cardio-renal-vascular lesions have replaced nearly all other causes of death, accounting for 87.5 per cent of the total. Nephropathy alone accounted for one-half of the deaths. The changing status with respect to causes of death was shown by the near disappearance of coma, sepsis and tuberculosis, formerly the chief causes of death. In this group they accounted for 0.6 per cent, 0.6 per cent, and 1.2 per cent. The median age at death was 32 and median duration 22 years.

DISCUSSION

Two major problems confront us: (1) the acceleration of vascular lesions; and (2) the progression of the diabetic process to a total diabetic state. Of the four possibilities which suggest themselves in the interrelationship of diabetes and vascular damage—(1) gene linkage, (2) physical signs, (3) a complication, or (4) any combination of these—our data support the last. The children of our diabetic mothers have shown the vascular pattern characteristic of diabetes. These individuals may be pre-diabetics; on the other hand, they are heterozygotes who may carry the vascular changes, hyperglycemia and/or glycosuria as part of the inherited recessive defect. Poor chemical control of diabetes markedly affected the vascular responses. Poor control has been reported in our cases[13] as showing a statistically significant correlation with the frequency and severity of vascular lesions in youth. Reversible vasomotor vascular changes can be seen in the bulbar conjunctiva. The end result of these abnormal reversible vasomotor changes is stasis, probably leading to hypoxia and starvation, sequelae, which, dependent upon degree and chronicity, will produce degenerative changes.

The presently available appropriate mixtures of regular and intermediate acting insulins in split doses have already increased the facility with which chemical control of juvenile diabetes can be achieved. Prescription of diets moderate in carbohydrate will also avoid the wide undesirable fluctuations of the levels of blood glucose.

The search for inhibitors of insulinase,[14] islet cell stimulators,[15] and technics for pancreatic grafts continues. Fifty per cent of a pilot group of former juvenile patients receiving estrogen during pregnancy showed a 50 per cent drop in insulin requirement contrasted with a 5 per cent drop in the diabetic males in this series. One fifteen-year-duration case so treated showed islet hypertrophy and hyperplasia (this case not included in the presently discussed autopsied reports).

Cortisone in small doses had no effect upon the natural course of diabetes in a group of young diabetic children. A group of adolescents have remained in the remission phase in a study of less than three years and are still sensitive to sulfonyl compounds.

Since November 1955 five patients, including one in this series, have had implants of the pancreatic tissue of their nonsurviving newborn infants. Sufficient time has not elapsed for proper conclusions to be drawn.

CONCLUSION

Of 1,072 juvenile diabetics surviving twenty years, 82 per cent are living. Their predisposition to diabetes was hereditary. Their disease followed a natural course from virulent onset to favorable remission to a total state. The problems of growth and development have largely resolved themselves. The successful control of former lethal factors—coma, sepsis and tuberculosis—is shown conclusively. Nephropathy has replaced other causes of death. Although new data on the possible mechanism of production of vascular damage and its regulation are suggested, poor chemical control of diabetes remains an important contributing factor. Present forms of available insulins control diabetes with greater facility than those used in this series of patients, and programs to alter the course of diabetes, especially those applicable in the remission phase, are in progress.

SUMMARIO IN INTERLINGUA

Curso Natural e Prognose de Diabete Juvenil

Ex un serie de 1.072 diabeticos juvenil qui ha supervivite vinti annos, 82 pro cento vive al tempore presente. Lor predisposition a diabete esseva hereditari. Lor morbo sequeva un curso natural ab declaration virulente a remission favorabile a un stato total. Le problemas de crescentia e de disveloppamento se ha resolvite in grande mesura. Le subjection de previemente letal factores como coma, sepsis, e tuberculose ha demonstrabilemente succedite. Nephropathia occupa le loco de altere causas de morte. Ben que nove datos relative al mechanismo possibile del production de lesiones vascular e etiam al regulation de ille mechanismo ha essite presentate, le inadequate adjustamento chimic de diabete remane un importante factor contributori. Le nunc disponibile formas de insulina es plus efficace in le regu-

lation de diabete que illos usate in le serie de patientes hic reportate. Programmas destinate a alterar le curso de diabete, specialmente durante le phase de remission, es in progresso.

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DISCUSSION

LAURANCE W. KINSELL, M.D., (*Oakland, California*): Dr. White, I enjoyed your paper very much. I wonder if you would have available the figures for insulin requirement in this group. The first six months, the first year, the second and third year following onset of diabetes.

ALLEN GOLD, M.D., (*Montreal*): Cortisone is mentioned as a beta cell protector. Would Dr. White care to elucidate this further?

REED HARWOOD, M.D., (*Boston*): I would like to ask Dr. White to tell us a little bit more about remissions in juvenile diabetics. Is it frequent for diabetics over twenty who have had severe onset of diabetes subsequently to get along without insulin for any time?

CECIL STRIKER, M.D., (*Cincinnati*): I would like to ask Dr. White whether there was any correlation between the need for increase in insulin and the high incidence of complications. For example, the incidence of those things that worry us, namely, kidney lesions.

HENRY T. RICKETTS, M.D., (*Chicago*): Dr. Striker's comments remind me of a comment I would like to make. Dr. White said, I believe, that as measured by glycosuria and hyperglycemia control in many of these patients was different, and I wondered what other measurements of control she would like to apply.

PRISCILLA WHITE, M.D.: I thought you were going to answer that last question, Dr. Ricketts.

I think that the juvenile patient, somewhere between the third and the fifth year of diabetes in almost all instances, becomes a total or near-total diabetic. The insulin requirement is high and remains high in these patients nearly all of whom did develop some vascular lesions.

I think these patients with relatively good control, of course, survive much longer. Our really bad actors have often died between the fifteenth and the twentieth year of their disease. The fact that they lived so long was partly an indication of relatively good control.

Cortisone was attempted in these fresh cases of diabetes preferably in their remission phase because of the experimental work of Houssay. In his experimental work on diabetic animals he found that if he gave, along with insulin, estrogen or cortisone, hydrocortisone, thyroxin, in very small doses, that within six months clinical evidence of diabetes had disappeared. When the pancreas was examined, hypertrophy and hyperplasia of islets was demonstrated.

We had, of course, been using large amounts of estrogenic nature in our former juveniles who subsequently became pregnant and thought that there was some indication of a drop in insulin requirement in these patients. One patient coming to autopsy did have hypertrophy and hyperplasia so that gave us the courage to try this experiment in the juvenile patients.

The remission phase of juvenile diabetes occurred in one-third of the patients in this long-term group, and I think that is a fairly good estimate of its frequency. In some patients the diabetes may have started in diabetic coma, and yet they will go into a remission phase. In some instances, the standard glucose tolerance test may become normal, and yet subsequently the disease becomes intensified, runs its natural course, and subsequently these patients later develop the vascular complications of the disease. I have a record of the insulin requirement of these long-term cases by yearly, six months' and three months' intervals.

Compounds Inhibiting Insulin Degradation

Robert H. Williams, M.D., and Frances L. Martin, M.S.,† Seattle*

In diabetics there is insufficient endogenous insulin action, yet in these patients rapid destruction of insulin-I^{131} has been demonstrated.[1, 2] Provision of exogenous insulin is inferior to an adequate endogenous supply since it is not subject to the same homeostatic responses and since it commonly provokes increased binding of insulin by plasma protein and occasionally marked insulin resistance. Inhibition of the degradation of insulin with consequent increase in the effectiveness of the supply available is a justifiable major goal, particularly if it can be accomplished by the oral administration of a safe compound acting for a sufficient interval. Many compounds have been demonstrated to inhibit insulin degradation in vitro[3, 4, 5, 6, 7] but relatively little has been reported relative to their effect in vivo, except for carbutamide and tolbutamide. Although these compounds have been shown to inhibit insulin degradation under certain conditions, the importance of this action clinically, compared to other actions, has not been established.

In this paper are reported the investigations, in vitro, of the inhibitory effect of a variety of compounds, most of which were sulfonamides, disulfides, thiazoles, thioureas or indoles.

METHODS

The details of the methods employed have been published;[7] they have been modified since an earlier report by Tomizawa et al.[4] The main phase of the study consisted of incubating insulin-I^{131} with a liver enzyme system which rapidly degraded insulin, as noted by measuring the increase in the amount of radioactivity soluble in trichloroacetic acid, and of determination of the extent to which various compounds inhibited insulin degradation.

This paper was presented in part at the Third Conference on Carbutamide sponsored by Eli Lilly and Company, Sept. 13-14, 1956.

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RESULTS

The major results are presented in the tables. It is observed in table 1 that 9 of the 10 sulfonamides, in the concentrations indicated, caused significant inhibition of insulin degradation. Most of the sulfonamides tested also had a thiazole radical. The greatest effect of the sulfonamides was shown by 6-ethoxy-2-benzothiazolesulfonamide. Butylaminobenzenesulfonylurea, butyltoluenesulfonylurea, isopropylaminobenzenesulfonamidothiadiazole and acetylaminothiadiazolesulfonamide (Diamox), all compounds that have been shown to have a hypoglycemic effect,[9, 10, 11, 12] showed a significant inhibitory effect. Another diuretic compound with a closely related structure (propionylaminothiadiazolesulfonamide) inhibited insulin degradation.

Of three nonsulfonamide thiazoles tested, aminomethoxyphenylthiadiazole was the most active (table 2). It is of note that the action of thiamine was comparable to that of the two sulfonylureas often used clinically for treating diabetics. Thiolthiazoline was inactive.

Seven of the eight disulfides tested were very active (table 3), the most active being biscarboxypropionylaminophenyldisulfide. Other very active disulfides were bisdimethylcarbamyldisulfide, bisaminophenyldisulfide, bisdimorpholinothiocarbamoyldisulfide, cystine, and lipoic acid. Among the four thioureas (table 4), dithiouracil and methoxybenzylthiosemicarbazide were definitely active. Other effective sulfur compounds were phthalazinedithiol sodium diethyldithiocarbamate, thiolhistidine, sodium heparinate and decamethylene-bisthiopseudourea (table 5).

The most active nonsulfur compound (table 6) was decamethylenebisguanidine (Synthalin A). This compound has been known for years to produce hypoglycemia.[13] The other more active nonsulfur compounds were: indolepropionic acid, methylindole, arbutin, indole, phenylbutyramide, phenylpropionic acid, and phenylacetic acid.

DISCUSSION

Previous reports have shown[3, 4, 5, 6, 7] that insulin degradation was inhibited by copper, zinc, p-chloromercuribenzoate, iodosobenzoate, iodoacetate, isopropylidene-2, 4-dithiohydantoin, various amino acids, auxins, peptides

TABLE 1

Results of incubation of insulin-I^{131} plus insulin-degrading enzyme system with and without test inhibitors (see footnote on page 454)

Inhibitor	mM/L.†	Average per cent inhibition	mM/L. causing 50 per cent inhibition‡
Sulfonamides			
6-Ethoxy-2-benzothiazolesulfonamide (U)	1.0	89	0.5
	<0.4	44	
$C_2H_5OC_6H_3SC(SO_2NH_2)N$	<0.1	13	
2-Acetylamino-1,3,4-thiadiazole-5-sulfonamide	30.0	97	6
	12.0	79	
	1.4	0	
$H_2NSO_2CNNC(NH\,COCH_3)S$			
2-Ethyl-5-p-aminobenzenesulfonamido-1,3,4-thiadiazole (SK)	10.0	46	11
	5.0	24	
	2.0	9	
$H_2NC_6H_4SO_2NHCNNC(C_2H_5)S$			
2-Isopropyl-5-p-aminobenzenesulfonamido-1,3,4-thiadiazole (Sch)	9.4	42	11.5
	1.0	14	
$H_2NC_6H_4SO_2NHCNNC(C_3H_7)S$			
2-Propionylamino-1,3,4-thiadiazole-5-sulfonamide (L)	4.0	35	12
	1.0	23	
$H_2NSO_2CNNC(NHCOC_2H_5)S$			
2-n-Butyrylamino-1,3,4-thiadiazole-5-sulfonamide (SK)	<2.5	30	ca.12
$H_2NSO_2CNNC(NHCOC_3H_7)S$			
N′-(6-dimethoxymethyl-4-methyl-2-pyrimidyl) sulfanilamide (S)	10.0	32	ca.12
$(CH_3O)_2CHCCHC(CH_3)NC(NHSO_2C_6H_4NH_2)N$			
1-n-Butyl-3-p-aminobenzenesulfonylurea§ (L)	46.0	76	15
	11.0	44	
$H_2NC_6H_4SO_2NHCONHC_4H_9$	2.0	24	
1-n-Butyl-3-p-toluenesulfonylurea§ (U)	11.0	100	2.5
	6.6	93	
$CH_3C_6H_4SO_2NHCONHC_4H_9$	2.2	47	
	0.9	13	
	0.2	0	
N′-(2-Thiazolin-2-yl)sulfanilamide (S)	<1.6	3	
$S(CH_2)_2NCNHSO_2C_6H_4NH_2$			

TABLE 2

Results of incubation of insulin-I^{131} plus insulin-degrading enzyme system with and without test inhibitors (see footnote on page 454)

Inhibitor	mM/L.†	Average per cent inhibition	mM/L. causing 50 per cent inhibition‡
Thiazoles			
2-Amino-5-(p-methoxyphenyl)-1,3,4-thiadiazole (S)	1.0	58	0.8
$CH_3OC_6H_4CNNC(NH_2)S$	0.25	20	
Thiamine hydrochloride	30.0	60	15
$HClNH_2CNC(CH_3)NCHCCH_2N(Cl)CHSC(CH_2CH_2CH)CCH_3$	10.0	45	
2-Thiol-2-thiazoline (U)	2.5	5	
$(CH_2)_2NC(SH)S$	1.0	2	

TABLE 3

Results of incubation of insulin-I^{131} plus insulin-degrading enzyme system with and without test inhibitors
(see footnote on page 454)

Inhibitor	mM/L.†	Average per cent inhibition	mM/L. causing 50 per cent inhibition‡
Disulfides			
Bis[2-(β-carboxypropionylamino)phenyl]disulfide (M)	0.01	100	0.002
	0.005	94	
	0.001	20	
$(HO_2C(CH_2)_2CONHC_6H_4S-)_2$	0.0001	17	
Bis(dimethylcarbamyl)disulfide (U)	0.025	100	0.011
	0.012	98	
$[(CH_3)_2NCOS-]_2$	<0.01	26	
Bis(2-aminophenyl)disulfide dihydrochloride (U)	<0.025	92	<0.015
	<0.01	30	
$(NH_2C_6H_4S-)_2 \cdot 2HCl$	<0.005	10	
	<0.002	4	
Bis(dimorpholinothiocarbamoyl)disulfide (U)	<0.2	100	<0.04
	<0.04	52	
$[O(CH_2CH_2)_2NNHCSS-]_2$			
Cystine	0.5	88	0.1
	0.13	54	
$(-SCH_2CHNH_2COOH)_2$			
DL-Lipoic acid	30.0	100	1.1
	10.0	95	
$CH_2CH_2CH_2(CH_2)_4COOH$	5.0	88	
| |	2.5	73	
S——S	0.5	33	
Bis(1-piperidinothiocarbamoyl)disulfide (U)	<1.0	27	
$(C_5H_{10}NNHCSS-)_2$			
Bis(p-nitrophenyl)disulfide (U)	<1.0	4	
$(O_2NC_6H_4S-)_2$			

TABLE 4

Results of incubation of insulin-I^{131} plus insulin-degrading enzyme system with and without test inhibitors
(see footnote on page 454)

Inhibitor	mM/L.†	Average per cent inhibition	mM/L. causing 50 per cent inhibition‡
Thioureas			
2,4-Dithiouracil (S)	1.0	98	0.5
	0.5	57	
NC(SH)NC(SH)CHCH	0.1	0	
1-p-Methoxybenzyl-3-thiosemicarbazide (S)	10.0	52	10
$CH_3OC_6H_4CH_2NHNHCSNH_2$			
1,3-Bis(p-methoxyphenethyl)-2-thiourea (S)	<1.0	11	
$(CH_3OC_6H_4(CH_2)_2NH)_2CS$			
3,5-Diiodo-4-hydroxybenzaldehyde,3-thiosemicarbazone (S)	<1.6	13	
$HOI_2C_6H_2CHNNHCSNH_2$			

TABLE 5

Results of incubation of insulin-I^{131} plus insulin-degrading enzyme system with and without test inhibitors (see footnote below)

Inhibitor	mM/L.†	Average per cent inhibition	mM/L. causing 50 per cent inhibition‡
Miscellaneous sulfur compounds			
1,4-Phthalazinedithiol (S)	0.5	100	0.04
	0.1	89	
$C_6H_4C(SH)NNCSH$	0.05	71	
	0.025	25	
Sodium diethyldithiocarbamate	10.0	100	<0.5
	2.0	91	
$(C_2H_5)_2NCS_2Na$			
L-2-Thiolhistidine	3.3	100	0.7
	0.45	32	
$NC(SH)NHCHCCH_2CH(NH_2)COOH$	0.1	25	
	0.06	0	
Sodium heparinate (U)	7.5	45	9
	2.5	23	
$C_{24}H_{33}N_2Na_7O_{35}S_5$	1.0	0	
2,2′-Decamethylenebis(2-thiopseudourea)dihydrobromide (S)	40.0	54	40
$HN=C(NH_2)S(CH_2)_{10}SC(NH_2)=NH \cdot 2HBr$			
2-Thiol-4-imidazoline (U)	<1.0	11	
$HSCHN(CH_2)_2NH$			
1-p-Methoxyphenyl-1,2,3-propanetrithiol (SK)	<0.2	13	
$CH_3OC_6H_4CH(SH)CH(SH)CH_2SH$			

We are very grateful for the compounds supplied by E. R. Squibb and Sons (S), by the Upjohn Co. (U), by the Smith, Kline and French Laboratories (SK), by Eli Lilly and Company (L), by Merck and Co. (M) and by Schering and Co. (Sch.).

†In many instances concentrations greater than those shown were tested but are not recorded either because lower concentrations caused maximal inhibition or because of very poor solubility in the media tested. Indeed, even a few of the compounds listed were not completely soluble at certain concentrations; the following sign < was used where a saturated solution of the inhibitor or a dilution prepared from the saturated solution was used. (In a similar study[7] with amino acids, 10^{-5} moles/ml. was erroneously labeled 10^{-2} moles/ml.)

‡The concentration of inhibitor necessary to give 50 per cent inhibition under the conditions of these experiments was obtained from a bi-logarithmic plot of per cent inhibition versus concentration of inhibitor. In most cases a linear relationship was observed and the 50 per cent value was read from the line. Where the data did not yield a straight line an approximation was made to obtain an estimate of the order of effectiveness of the various inhibitors. For the weakest inhibitors no such evaluation was attempted.

§Results of study of these two compounds have been reported previously.[8]

TABLE 6

Results of incubation of insulin-I^{131} plus insulin-degrading enzyme system with and without test inhibitors
(see footnote on page 454)

Inhibitor	mM/L.†	Average per cent inhibition	mM/L. causing 50 per cent inhibition‡
Nonsulfur compounds			
Decamethylene-bis(guanidine) $NH_2CNHNH(CH_2)_{10}NHNHCNH_2$	7.0 2.8 1.0	66 30 28	5
Indole-3-propionic acid $C_6H_4C(CH_2CH_2COOH)CHNH$	10.0 6.0	84 39	7
5-Methylindole $CH_3C_6H_3CHCHN$	2.5 0.8 0.27	34 24 6	8
Arbutin $HOC_6H_4OCH(CHOH)_3CHCH_2OH$	10.0 2.5 1.0	53 25 20	9
Indole $C_6H_4CHCHNH$	<30.0 3.0	70 32	11
2-Phenylbutyramide (U) $C_2H_5CH(C_6H_5)CONH_2$	10.0 5.0 2.0	42 28 17	14
3-Phenylpropionic acid (U) $C_6H_5CH_2CH_2COOH$	30.0 10.0 2.5	60 34 10	22
Phenylacetic acid $C_6H_5CH_2COOH$	30.0 10.0	49 22	30
α-(Dimethylaminomethyl)-1-ethyl-3-indolemethanol (U) $C_6H_4CH[CH(OH)CH_2N(CH_3)_2]CH{-}NC_2H_5$	<1.0	15	
3-(2-Aminoethyl)-5-indanol · creatine sulfate · hydrate (U) $HOC_6H_3C(CH_2CH_2NH_2)CHNH$	6.2 1.2	14 0	
Phenylalanine $C_6H_5CH_2CHNH_2COOH$	23.0 7.8	23 13	
3-Acetamido-5-methyltetronic acid (U) $H_3CCHC(OH)C(NHCOCH_3)COO$	10.0 5.0	18 6	
L-Leucine $(CH_3)_2CHCH_2CHNH_2COOH$	25.0 5.0	2 0	
5-Ethyldialuric acid (S) $C_2H_5C(OH)CONHCONHCO$	10.0	0	
L-Proline $NH(CH_2)_3CHCOOH$	30.0	0	

and proteins. The mechanism by which these compounds and the ones reported here inhibit the degradation of insulin is not known. Since reduction may play an important role in inactivation of the hormone it may be that some of the agents, particularly the disulfides, may spare insulin by acting as substrates for reducing agents. Another explanation may be that of de Barbieri and Grassi[14] who postulated that the insulin-degrading enzyme is a peptidase in which sulfhydryl groups play an essential part for activity and that when its sulfhydryl groups are oxidized by disulfides, the enzyme is inactivated. In case of compounds like phenylacetic acid it may be postulated that by combining with certain components of the insulin-degrading enzyme system degradation of the hormone is inhibited.

Some compounds may inhibit markedly the degradation of insulin in vitro yet exert no significant effect in vivo. Therefore in evaluating their possible usefulness in the treatment of diabetes it is important to determine their capacity to lower the blood sugar; such studies are in progress.

SUMMARY

Using an in vitro system consisting of a liver enzyme preparation which rapidly degrades insulin-I^{131}, it has been found that many different compounds inhibit the degradation of the hormone. Among the inhibitors are certain sulfonamides, disulfides, thiazoles and thioureas. Other types of sulfur compounds had a significant activity in the following order: phthalazinedithiol, sodium diethyldithiocarbamate, thiolhistidine, sodium heparinate, and decamethylenebisthiopseudourea. The most active nonsulfur compounds were, respectively: decamethylenebisguanidine, indolepropionic acid, methylindole, arbutin, indole, phenylbutyramide, phenylpropionic acid and phenylacetic acid.

The mechanisms by which the compounds inhibit degradation and their effectiveness in lowering blood sugar are being investigated.

SUMMARIO IN INTERLINGUA

Compositos Que Inhibi le Degradation de Insulina

Per medio de un systema in vitro consistente de un preparato de enzyma hepatic que produce un rapide degradation de insulina a I^{131}, il esseva constatate que multe differente compositos inhibi le degradation del hormon. Le inhibitores include certe sulfonamidos, bisulfidos, thiazoles, e thioureas. Altere compositos de sulfure possede significative grados de activitate in le sequente ordine: Phthalazinedithiol, diethyldithiocarbamato de natrium, thiolhistidina, heparinato de natrium, e decamethylenebisthiopseudourea. Le plus active compositos non-sulfuric esseva: Decamethylenebisguanidina, acido indolepropionic, methylindol, arbutina indol, phenylbutyramido, acido phenylpropionic, e acido phenylacetic.

Le mechanismo per que le compositos inhibi le degradation de insulina e lor efficacia in reducer le nivellos de sucro sanguinee es sub investigation.

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Insulin Resistant Diabetes with Insulin Antibodies

A Case Report

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Diabetes is considered to be insulin resistant when the patient fails to respond to ordinary doses of insulin.[1] Insulin resistance may occur in infection, liver disease, hyperthyroidism, hyperadrenocorticism, and hyperfunction of the anterior lobe of the pituitary. Lerman[2] was the first to postulate, and Lowell[3] the first to demonstrate, insulin neutralizing antibodies in the serum of insulin resistant diabetics. The importance of immune reactions in insulin resistance was emphasized by Lukens.[4]

Goldner and Ricketts[5] noted the association of insulin refractoriness with insulin allergy while Root[6] related both phenomena to the occurrence of antibodies against insulin. Lowell[7] related the allergic insulin reactions to the presence of skin sensitizing antibodies, different from insulin neutralizing antibodies.

The present study is concerned with a case of insulin resistant diabetes in which both insulin blocking antibodies and skin sensitizing antibodies could be demonstrated in the serum.

REPORT OF CASE

N. K., a 49-year-old woman known to have had diabetes since 1953, was admitted to the medical department in February 1955.

After a short febrile disease her diabetes became more severe, the fasting blood sugar reaching 380 mg. per 100 ml., with 10 per cent glucose in the urine and ketonuria. She had received regular and protamine-zinc insulin with interruptions since the diabetes had been diagnosed. Her past history revealed no allergic phenomena, and she had not received blood transfusions.

Physical examination was essentially normal. The temperature was normal, the blood pressure was 150/90 mm. Hg. Gynecologic, ophthalmologic, and neurologic examinations did not reveal abnormal findings. On admission the urine contained a large amount of glucose and acetone; there was no albuminuria, the sediment was normal and a urine culture was negative. Blood examination showed normal hemoglobin value and cell counts and a normal sedimentation rate. The fasting blood sugar was 280 mg. per 100 ml., urea 48 mg. per 100 ml., cholesterol 300 mg. per 100 ml., total serum protein 6.73 gm. per 100 ml., albumin 3.70 gm. per 100 ml., globulin 3.03 gm. per 100 ml.; routine liver function tests were normal. Blood cultures were negative.

Urinalysis showed normal values for 17-ketosteroids (6.8 mg.), 11-oxysteroids (1.45 mg.), estrogens (25 units) and FSH (100 units) per 24 hours. The basal metabolic rate was plus 20 per cent. Roentgen examinations of the skull, sella turcica, and gastrointestinal tract, cholecystography and intravenous pyelography gave normal results. Electroencephalography (repeated eight times) constantly showed remarkable bilateral, mainly frontal disturbances, slightly accentuated on the left side.

Course in hospital

During the first few days after admission the patient was treated with 60 units of regular insulin per day and a diet containing 50 gm. of carbohydrate, 70 gm. of protein and 70 gm. of fat. On this regime she excreted 70 gm. of sugar per day. The daily insulin dose was increased gradually to a maximum of 850 units. Even with such a dose, hypoglycemia did not occur; the daily urinary sugar varied from 16.0 to 102 gm. and the blood sugar from 220 to 514 mg. per 100 ml. There was no difference in glucose excretion whether local insulin (Galma) or imported (Boots or Organon) was used.

A 24-hour interruption of insulin treatment, necessary

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for the performance of the Lowell mouse test, caused the blood sugar to rise to 560 mg. per 100 ml.; acetone appeared in the urine, and 170 gm. of glucose was excreted in twenty-four hours.

When the administration of 850 units per day was resumed, blood sugar values dropped to 231 mg. per 100 ml., and the daily glucose excretion to 30-40 gm. after about one week. Acetonuria disappeared within three days.

Intravenous infusions of ACTH, 10 mg. daily for two weeks, caused marked improvement, and insulin could be reduced to 430 units per day. On further reduction of insulin, however, sugar excretion increased.

During a subsequent period of two weeks BAL (dimercaptopropanol) was administered intramuscularly, 100 mg. twice per day, while ACTH was discontinued. During this period insulin could be reduced to 200 units per day without increase of sugar excretion.

In July 1955, the patient was discharged from the hospital in satisfactory condition with 300 units of insulin daily and a diet consisting of 150 gm. of carbohydrate, 70 gm. of protein and 70 gm. of fat.

The patient was re-hospitalized twice during 1955, once in August after a short upper respiratory infection which caused aggravation of the diabetes. On admission 75 gm. glucose and a positive acetone reaction were found in the twenty-four hour urine collection. After administration of 1,500 units of insulin within the first eighteen hours, acetone disappeared from the urine and glucose excretion dropped to 20 gm. per day. During the next twenty-one days, 500-620 units of insulin per day were administered, and the patient was discharged after forty-four days with 300 units of insulin per day, excreting 5 gm. of sugar in the urine per day, which was free of acetone.

On the second admission, in October 1955, glucose excretion amounted to 40 gm. per day and acetone was again present, the increase occurring without previous infection. Daily administration of 600 to 700 units of insulin, combined with infusions of 10 mg. of ACTH during fourteen days, caused marked improvement. Subsequently cortisone was given, 200 mg. daily for six days and then in gradually diminishing doses to 25 mg. per day.

On discharge the patient excreted 0 to 2.5 gm. glucose per day and had no acetone in the urine. On the day of discharge the fasting blood sugar was 246 mg. per 100 ml. She was instructed to take 300 units of insulin daily and 25 mg. of cortisone every second day and a diet as before.

SPECIAL INVESTIGATIONS

a. *Glucose and insulin tolerance tests*

Fasting blood sugar levels were determined at thirty-minute intervals for three hours after the intravenous injection of 20, 40, or 60 units of regular insulin. Figure 1 shows that the blood sugar values decreased only slightly, the decrease in the first half hour being less than 50 per cent.[8]

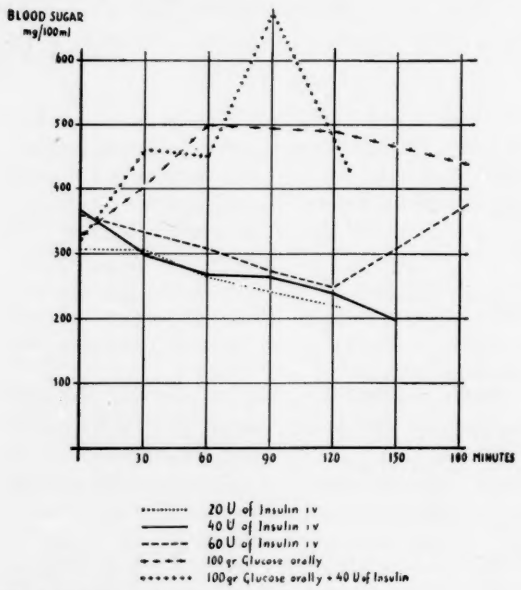

FIG. 1. Glucose and insulin tolerance tests.

In addition, a glucose-insulin tolerance test was carried out. Blood sugar values were determined just before and at thirty-minute intervals for three hours after the simultaneous administration of 100 gm. of glucose (orally) and 40 units of insulin intravenously. The resulting blood sugar values, compared with those obtained after the oral administration of 100 gm. glucose without insulin, show that insulin had no effect on the blood sugar.

b. *Lowell mouse test*

The Lowell mouse test was performed according to Eskind, Franklin and Lowell.[9] The ED_{100} of local insulin (Galma) (smallest quantity of insulin producing hypoglycemic signs such as paralysis of hindlegs and convulsions in 100 per cent of the animals tested) for 20 gm. mice was found to be 0.1 unit.

Mixtures of 0.1 unit of insulin with varying amounts (0.25-1.5 ml.) of normal human serum, of the patient's serum, and of physiologic saline were prepared. Suffi-

cient glucose was added to the normal serum and to the saline to produce glucose concentrations equal to those in the patient's serum. The mixtures were incubated at 37° for one hour and injected intraperitoneally.

Table 1 shows that 1.5 ml. of the patient's serum protected the animals completely from the hypoglycemic action of insulin. With decreasing amounts of the patient's serum the protective effect diminished.

TABLE 1

Lowell mouse test
Intraperitoneal injection of 0.1 U of insulin, preincubated with serum

Mixture ml. injected	No. of mice showing hypoglycemic signs per total injected: Patient's serum + insulin	Normal serum + insulin	Saline + insulin
1.5	0/5	5/5	5/5
1	1/5	5/5	5/5
0.75	2/5	4/5	5/5
0.50	4/5	5/5	5/5
0.25	5/5	5/5	5/5

c. *Rat diaphragm glucose uptake and glycogen synthesis*

The inhibitory effect of the patient's serum on the enhancing influence of insulin on glucose utilization and glycogen synthesis by rat diaphragm was tested by the method of Gemmill.[10]* The action of insulin after incubation with the patient's serum, was compared with the action of insulin incubated with normal serum to which glucose had been added to match the concentration in the serum of the patient.

The addition of 0.1 unit of insulin to a rat diaphragm preparation evoked more than twofold increase of glucose utilization (table 2). Previous incubation of insulin with the patient's serum abolished this effect.

Glycogen synthesis by rat diaphragm, incubated with normal human serum, was greatly enhanced by the addition of 0.025 unit of insulin. In the presence of the patient's serum this amount of insulin had no such effect. Addition of 0.1 unit of insulin, however, produced increased glycogen synthesis even after incubation with patient's serum.

d. *Demonstration of antibodies to insulin by red cell agglutination*

Sheep red blood cells were treated with a 1:20,000 tannic acid solution, and insulin was conjugated to the red cells by the method of Stavitsky and Arquilla.[11, 12] When the undiluted patient's serum or a 1:1 dilution

*The diaphragm tests were kindly carried out by Prof. E. Wertheimer, Department of Biochemistry, The Hebrew University Medical School, Jerusalem.

TABLE 2

Rat diaphragm test

Insulin units	Glucose utilization mg./100 mg. diaphragm: Normal serum	Patient's serum	Glycogen synthesis mg./100 mg. diaphragm: Normal serum	Patient's serum
0.	0.53	0.87	0.070	0.030
0.025	—	—	0.124	0.036
0.1	1.19	0.92	0.190	0.140

Glucose concentration patient's serum: 380 mg. per 100 ml.

Glucose concentration normal serum: 100 mg. per 100 ml.

plus additional 280 mg. per 100 ml. = 380 mg. per 100 ml.

of this serum in physiologic saline was added to such treated red cells, hemagglutination resulted, demonstrating the presence of insulin antibodies. Control experiments with normal serum and the patient's serum with untreated red cells were negative.

e. *Skin sensitizing antibodies*

Active and passive transfer skin tests were performed. In the active skin test a quantity of 0.1 units of insulin was injected intradermally and the whealing effect compared with that of a control injection of physiologic saline solution. A positive reaction to insulin was observed (table 3). Similar injections of insulin did not produce any whealing effects in normal persons.

A passive transfer test, performed according to Prausnitz-Küstner by injecting insulin intradermally into a normal person who had received an intradermal injection of the patient's serum at the same site twenty-four hours previously, was strongly positive (table 3). Controls with normal serum were negative.

f. *Electrophoresis of patient's serum*

Electrophoresis on filter paper of the serum of the patient was carried out on Whatman No. 1 filter paper,

TABLE 3

Skin sensitizing antibodies

Substances injected intracutaneously	Active skin sensitivity test: Patient	Normal	Passive transfer test: Normal
Insulin	+++	—	—
Saline	—	—	—
Insulin 24 hrs. after patient's serum			+++
Insulin 24 hrs. after normal serum			—

— no wheal produced.

+++ wheal of 2 cm. diameter produced after 20 min.

in a veronal-Na acetate buffer, *p*H 8.6, ionic strength 0.1, duration sixteen hours, current 4 volt/cm., staining with amidoblack 10 B. No increase of gamma globulin was found (19.2 per cent of total serum protein, normal range 13-25 per cent). The β-globulin value was slightly increased (18.2 per cent, normal range 10.5-16.3), while α_2 globulin was decreased (5.4 per cent, normal range 9.0-15 per cent).

DISCUSSION

The insulin resistance in this patient could be related to the presence of an insulin antibody in her serum. No disturbances of thyroid, adrenal, anterior pituitary, or liver functions were found, and although the patient suffered from repeated infections the insulin resistance persisted after their cure. Electroencephalographic disturbances have been described in cases of unstable diabetes.[13] Although aberrations of the electroencephalogram had been observed repeatedly in the present patient, their possible relationship to the insulin resistance has not been established.

The presence of an insulin neutralizing factor, already suggested by the weak response to insulin in the tolerance tests, was proved by the Lowell mouse test.

The rat diaphragm test performed with the patient's serum showed an inhibitory effect on insulin action similar to the findings of Marsh and Haugaard[14] who examined the serum of an insulin resistant diabetic. However, the insulin inhibitory action of the serum of our patient could be demonstrated only when relatively small quantities of insulin were applied in the test and could be overcome by adding more insulin.

Lowell[7] suggested that the insulin neutralizing activity of insulin resistant diabetics, as demonstrated with the mouse test, is due to insulin neutralizing antibodies. Evidence for the presence of insulin antibodies in the serum of the present case was obtained by the positive active and passive transfer skin tests and by the agglutination of insulin-sensitized tannic acid treated sheep erythrocytes.[11, 12] Infection and intermittent use of insulin, both considered conducive to the development of insulin antibodies,[6, 18] may have been factors in the production of insulin resistance in our patient. There is no proof, however, that the insulin neutralizing factor and the insulin antibodies, as demonstrated in the skin and hemagglutination tests, are identical.

Jorpes[15] doubted the existence of skin sensitizing insulin antibodies in cases of insulin allergy, as he successfully prevented allergic reactions to insulin in a hypersensitive patient by the use of a recrystallized commercial insulin preparation. Loveless and Cann[16] demonstrated that the skin sensitizing insulin antibodies and the insulin neutralizing serum factor are present in different serum protein fractions, the former in the beta globulin fraction, the latter closely bound to the gamma globulin fraction. Sehon and co-workers,[17] using zone electrophoresis, reported an increase of serum gamma globulin in a case of insulin resistant diabetes. In our patient whose serum contained both skin sensitizing insulin antibody and insulin neutralizing factor, electrophoretic examination showed normal gamma globulin. The slightly increased beta globulin value might be due to high cholesterol content.

When very high doses of insulin were administered to our patient, ketonuria disappeared and glucose excretion decreased. Parallel to this were the results of the rat diaphragm test in which large doses of insulin overcame the insulin inhibitory effect of serum. It may be assumed that part of the insulin administered was engaged in the inactivation of the insulin neutralizing factor, the remainder of the insulin manifesting its normal action on carbohydrate metabolism. The results of the mouse test are in agreement with such a supposition. Inhibition of the action of insulin was observed as long as a sufficient quantity of serum was used.

As to the value of the use of corticotropin or corticosteroids in the treatment of insulin resistant diabetes, opposite results have been reported. Loveless and Cann[16] and Kaye, McGarry and Rosenfeld[18] reported that corticotropin administration markedly aggravated the diabetic state, whether given during a period of relatively low insulin requirement (160 units per day), or of very high requirement (900-1100 units per day). Our results, on the other hand, are in agreement with those of Howard,[19] Gitelson,[20] and Kleeberg, Diengott and Gottfried[21] who obtained improvement with ACTH.

It is known that alloxan induced experimental diabetes is accompanied by a temporary fall of blood glutathione,[22, 23] and that alloxan diabetes can be prevented by the administration of glutathione.[24] Furthermore, hyperglycemia induced by corticotropin can be reduced by intravenous glutathione.[25] These observations prompted Butterfield[26] to administer the SH compound BAL (dimercaptopropanol) in two cases of insulin resistant diabetes with an apparent improvement of the glucose tolerance. The effect of BAL treatment in the present case of insulin resistant diabetes is in agreement with these observations.

SUMMARY

A patient with insulin resistant diabetes is described who required up to 1,500 units of insulin per day for

control of glycosuria and acetonuria.

No endocrinologic or metabolic disturbances were found that could explain the insulin resistance.

An insulin neutralizing factor in the serum of the patient was demonstrated by the Lowell mouse test and by the rat diaphragm test, measuring glucose uptake and glycogen synthesis.

The serum contained skin sensitizing antibodies and an antibody which agglutinated insulin-coated tannic acid treated red blood cells. Paper electrophoresis did not show increased gamma globulin values.

SUMMARIO IN INTERLINGUA

Diabete Insulino-Resistente con Anticorpores a Insulina: Reporto de un Caso

Es describite un patiente con diabete insulino-resistente, qui requireva usque a 1500 unitates de insulina per die pro le dominio de su glycosuria e acetonuria.

Esseva trovate nulle disturbationes endocrinologic o metabolic que haberea explicate le resistentia a insulina.

Un factor insulino-neutralisante esseva demonstrate in le sero del patiente per medio del test de Lowell a muses e del test a diaphragma de ratto, que mesura la acceptation de glucosa e le synthese de glycogeno.

Le sero contineva anticorpores cuti-sensibilisante e un anticorpore que agglutinava erythrocytos tractate con acido tannic e revestite de insulina. Electrophorese a papiro non monstrava augmentate valores de globulina gamma.

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The Personality and Intelligence of Diabetics

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BACKGROUND

Considerable conflicting evidence has been published concerning both the intelligence and personality of diabetics. Much evidence, pro and con, has been brought forth to show that the diabetic exhibits particular abnormalities of personality, or reacts abnormally under certain stress conditions. The majority of evidence is clinical, involving few cases, and only suggestive of the actual diabetic personality situation. The problem of the intelligence of diabetics has been attacked by a number of investigators with varying results.

Psychological studies relating to the diabetic may be categorized as follows:

1. Studies attempting to show an emotional basis for the onset of the disease. They do not always suggest that a particular personality pattern is involved.
2. Studies attempting to show that recurrent acidosis and diabetic regulation, in general, have an emotional basis.
3. Studies showing that diabetics have a particular personality pattern differentiating them from normals or other disease groups.
4. Studies relating to the mental ability of the diabetic.

In the first category are studies by Daniels, [6, 7] Mirsky,[25] Hinkle and Wolf,[17] Bruch,[4] and Gendel and Benjamin.[2] Of these authors, Daniels, Mirsky, and Hinkle and Wolf agree that emotional factors and stress play an important role in the onset of diabetes. Bruch, in psychiatric observations of thirty-seven diabetic children found no evidence for such a relationship. Gendel and Benjamin,[12] investigating the hypothesis that the stress of wartime might increase the incidence of diabetes, concluded after World War II that "in no case was it possible to prove a direct causal relation between the stress incident to military service and subsequent development of permanent diabetes." Since most of us are exposed to various "stresses" during our lives without developing diabetes, a particular personality or biologic pattern may predispose to the development of the disease. The particular personality syndrome, if any, that diabetics have in common remains to be demonstrated.

With regard to emotions and the ease of diabetic control and the development of acidosis, Rosen and Lidz[27] concluded that emotional factors were at most secondary in importance in patients repeatedly admitted in diabetic acidosis. Daniels[7] contradicts these findings and reports that emotions play an important role. Hinkle and Wolf[17] provide quantitative support for the contention that diabetics react in an exaggerated manner physiologically when stress is introduced.

As to the occurrence of a characteristic diabetic personality, Hofman-Bang[18] describes what is said to be the first true case of the often suspected relationship between schizophrenia and diabetes mellitus. Clinical studies summarized by Lindberg,[20] led to the conclusion that "there exists a clear-cut clinical picture of the disease (diabetes mellitus) which justifies the name of diabetic psychosis." Menninger[24] in 1935 stated that depression and anxiety are characteristic personality patterns of the diabetic. McGavin and co-workers,[23] in 1940, found 32 of 49 diabetic children who were considered "maladjusted." In a later study by Loughlin and Mosenthal,[22] two factors were found to be associated with abnormalities of personality: a) an early onset of diabetes, and b) frequent ketosis.

A longitudinal study by Fischer and Dolger[11] reported on the observations of forty-three diabetics over a 10-20 year period. Psychopathic behavior was exhibited in three patients with other minor behavior disturbances being more frequent. They concluded only that "diabetes mellitus produces many psychologic problems which may result in abnormal behavior. . ." A similar conclusion that diabetics tend to have more

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adjustment problems than nondiabetics of comparable age was reached by Eisele.[9]

A study by Boulin and others[2] showed that 19 of 30 diabetic children had behavioral abnormalities. Six had psychomotor instability, five had anxiety psychasthenia or melancholia, four were troublesome and aggressive and four were classified egocentric. Projective tests were used in studying personalities.

Dunbar[8] has been especially positive in the assertion that the diabetic has specific behavioral patterns which differentiate him from other disease groups. She and her associates have stated that, among other things, the diabetic is characterized by a conflict between hatred and submission to the parents, inadequate sexual adjustment marked by anxiety, homosexual tendencies, nervousness, depression, and paranoid suspicion.

The most recent study reported is that of Bennett and Johannsen.[1] They and their co-workers studied fifty-eight children from 7 to 10 years of age in a summer camp for diabetics. All children were given the Children's Apperception Test, Michigan Picture Test, Rosenzweig Picture-Frustration Test, the Rorschach, and the Goodenough Draw-A-Man Scale of Intelligence. They reached no conclusions, but their results were presented in the form of tentative hypotheses suggesting a relationship between personality and various factors such as duration of diabetes, insulin dosage, glucose content of urine, insulin reactions, parental control, socio-economic status, and sex differences.

A number of studies can be cited in which no characteristic diabetic personality is indicated. Brown and Thompson[3] in 1940 asserted that the diabetic exhibits no characteristic personality pattern. Lisansky,[21] in 1948, used the Rorschach to show that the diabetic has a drive for achievement but limited productivity, tendencies to constriction and withdrawal, and conflict in his tendencies to be outgoing and withdrawing. She concluded, however, that there was no personality picture typical of the diabetic. Bruch,[4] in the previously cited psychiatric study, could discover no uniform psychological pattern in the diabetic. In a study published by Crowell[5] the personality patterns of diabetics were compared with those of rheumatic fever cases in order to test the Dunbar hypothesis that these two disease entities are characterized by different personality patterns. Using the Rorschach Ink Blot Test, and the Minnesota Multiphasic Personality Inventory (MMPI), he studied 25 patients with diabetes and 28 with rheumatic fever. He found practically no evidence of distinguishing behavior patterns specific to the two diseases. He also demonstrated no personality differences between good and poor control diabetics.

The intelligence of diabetics, too, has received considerable attention in the literature. Much controversy has arisen over this relatively simple assessment. The confusion has been attributed to biased sampling. Researchers showing the diabetic with higher than average intelligence, West,[32] Joslin,[19] and Grishaw,[14] have been accused of taking their sample from a high socio-economic bracket. Teagarden,[29] Shirley and Greer,[28] and Boulin and others[2] have reported below average intelligence. Studies by Brown and Thompson,[3] Fischer and Dolger,[11] Lisansky,[21] McGavin and others,[23] and Wagner and others,[31] report normal intelligence.

PROBLEM AND PROCEDURE

The present study was designed to provide additional evidence relative to these diabetic intelligence and personality problems. The diabetic population here reported consisted of juvenile diabetics (i.e., onset of diabetes prior to age sixteen) who had been treated at the Children's Hospital of Pittsburgh. The sample, based upon hospital records, was selected from among those who are living in the Pittsburgh area.

The personality testing instrument used was the individual card form of the Minnesota Multiphasic Personality Inventory (MMPI).[15] The MMPI is a widely recognized objective measure of personality. It consists of 550 cards on each of which is a statement that the subject classifies as "true," "false," or "cannot say." The test covers a wide range of personal subject matter ranging from the individual's physical condition to his social attitudes and morale. Its scales were derived from psychiatric practice, and it provides scores on all the clinically more important phases of personality. The instrument is unique in that it has several validity scales. These give information concerning the subject's truthfulness, carelessness, and psychological defensiveness. In addition to the MMPI, each diabetic was given the Stanford-Binet, an individually administered standard test of mental ability.[30]

Individual appointments were arranged by telephone. Subjects were told that the hospital was making a follow-up study of all diabetics who had been patients at Children's Hospital. Most of the subjects, especially in the younger age groups, were assured that there would be no injections, or drawing of blood, and that the whole procedure would consist of answering questions in an interview. Every attempt was made to have them feel obligated, thus giving them little opportunity to evade the interview. This was done to avoid the bias of using only volunteers. No mention was made

that we were measuring personality and intelligence. If he asked, the subject was told that we were trying to understand a little more about how the diabetic thinks and feels. Four of the selected cases were lost, and these largely due to difficulties in their getting time off from work.

It was felt that the sample consisted of a representative socio-economic range of the diabetics from this hospital. A bias was introduced in the personality testing when several cases were either unable to work with the MMPI due to low mental ability, or showed invalid profiles. All of these cases, however, were included in the intelligence testing sample.

The following table summarizes the characteristics of the MMPI sample.

TABLE 1
Characteristics of diabetic MMPI sample

	Males N=20		Females N=20	
	Mean	S.D.	Mean	S.D.
Age tested (years)	17.7	2.8	19.9	4.0
Age onset (years)	8.7	4.6	9.8	3.9
Intelligence (I.Q.)	110	11.1	107	15.0

RESULTS

All scores on the MMPI are reported as standard "T" scores which have a mean of 50 and a standard deviation of 10. Mean scale scores for the diabetic group are reported in table 2. Inventory norms are based upon adult normals with a wide age range.

TABLE 2
"T" scores on the MMPI scales (N=40)

	Mean	S.D.
Hypochondriasis (Hs)	49.5	8.9
Depression (D)	51.4	7.7
Hysteria (Hy)	52.6	8.8
Masculinity-femininity (Mf)	50.7	9.6
Paranoia (Pa)	52.4	7.8
Psychasthenia (Pt)	52.6	7.6
Social introversion-extroversion (Si)	50.1	7.8
Psychopathic deviate (Pd)	57.4	6.2
Schizophrenia (Sc)	55.0	8.6
Hypomania (Ma)	60.6	10.8

As is evident from the table, several scales show marked differences from the adult norm ("T" = 50). This is especially true on the psychopathic deviate (Pd), schizophrenia (Sc), and hypomania (Ma) scales. The clinical implications of these scales are that these subjects may tend to be rebellious with aggressive asocial and amoral tendencies (Pd), schizoid, or bizarre in their verbal associations (Sc), and overactive and impulsive (Ma). At first glance it would appear that these findings may support the contention that the diabetic has abnormal behavioral tendencies.

Since the test norms do not contain adequate representation of the late adolescent and early adult age range of our sample, it was necessary to turn to controls approximating this age range. These were found in the MMPI literature. The first group of controls was reported by Monachesi[26] and consisted of 56 male and 79 female nondelinquents. Median age of the group was 16.2 years, and median I.Q. reported was 108. The group, although slightly younger than the diabetics here reported, had approximately the same mental ability. Another control group consisting of 160 college freshmen and sophomores was reported by Gilliland and Colgin.[13] Although mean age and intelligence are not reported, it is probable that they approximate the diabetic sample. Figure 1 shows profile comparisons of the diabetic and control populations. The data of Crowell,[5] although using the MMPI with twenty-five diabetics having an average age of nineteen years, is also included in figure 1 for comparison. From this figure it is evident that the differences which are apparent when diabetics are compared with adult normals on the MMPI disappear when they are compared with controls more closely approximating their own characteristics.

Seven of the nine scales showed the mean scores of the control groups to be equal or more deviant than the diabetics. On the remaining scales on which the diabetics were more deviant, Pd (rebellious and psychopathic tendencies), and Ma (restlessness and overactivity), the differences are not statistically significant.

Since Loughlin and Mosenthal[22] have indicated that an early onset of diabetes is associated with abnormalities of personality, product-moment correlations between age of diabetic onset and scores on the MMPI scales were computed. Scores on each of the scales were compared to onset age. If a correlation was positive, then those individuals who were older at diabetic onset would have larger abnormal deviations on one or other of the MMPI scales. For a negative correlation, the reverse of this is true. These correlations ranged from −.27 to +.30. Neither of these extremes is statistically significant.

In addition to the preceding MMPI group, the Stanford-Binet test of intelligence was administered to another larger sample of diabetics including Children's Hospital patients, and adult diabetics reporting to a nearby clinic and hospital. This sample of fifty-eight diabetics ranged in age from 7 to 63 years with a mean of 20.8 years.

The Stanford-Binet test indicated that the mean intelligence of the group of 58 diabetics was 103 with a standard deviation of 18.9. The average range on this test in terms of national norms is 90-110. Thus these

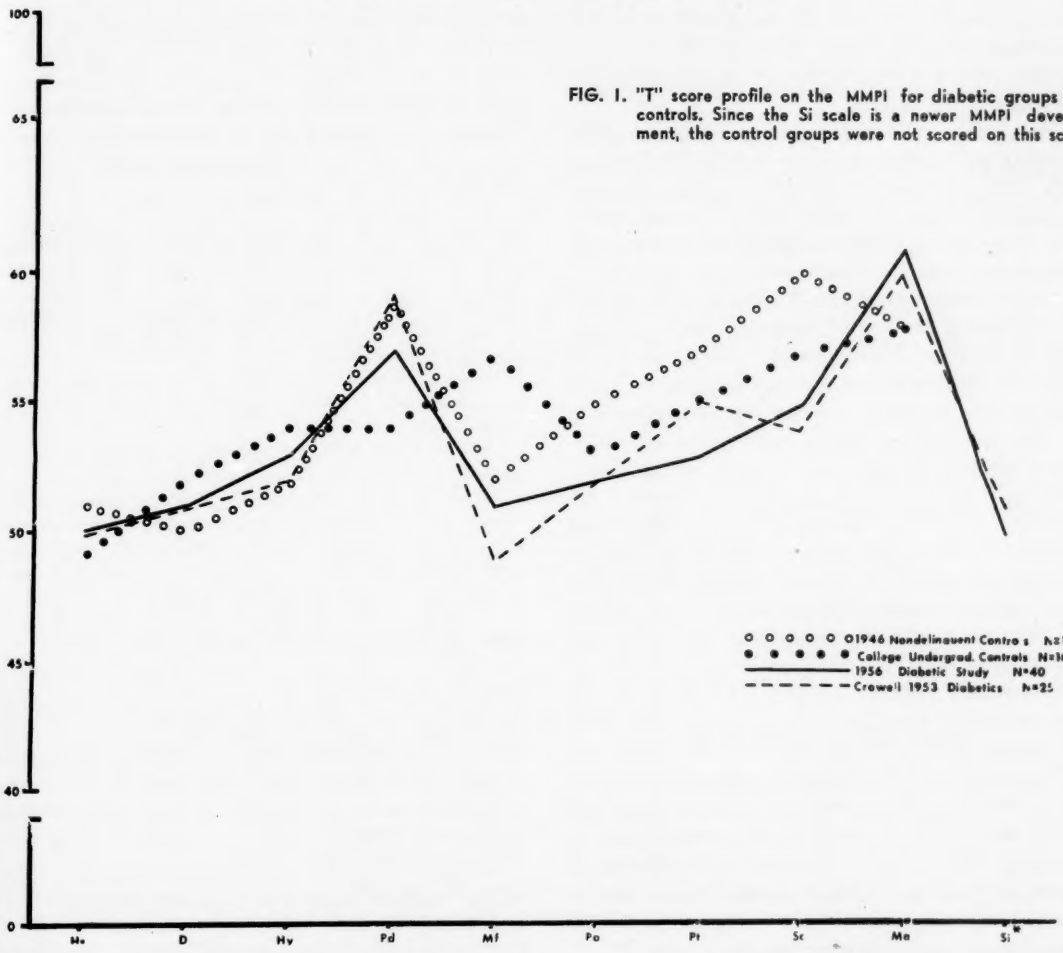

FIG. 1. "T" score profile on the MMPI for diabetic groups and controls. Since the Si scale is a newer MMPI development, the control groups were not scored on this scale.

diabetic patients demonstrated no difference in I.Q. from the accepted norms.

DISCUSSION

If there is a particular personality pattern that the diabetic manifests, as has been suggested,[8] this should appear in a profile analysis. The figure 1 profiles demonstrate no significant difference between diabetics and controls when subjects of approximately the same age are compared. It should be noted that the results from the two independent diabetic studies show closely similar findings.

Diabetics in this study are compared with normal populations. It must be remembered that no attempt has been made to provide controls for the daily regimen to which the diabetic must adhere. Also, no allowance is made for the fact that these patients periodically visit a clinic or private physician, or that they were asked to take time out of their daily routine to provide many details of personal information. Since controls with the foregoing characteristics were not used and no significant differences were demonstrable, it appears that the diabetic compares very favorably in terms of personality normality. It may be that the abnormalities which a number of investigators have noted and generalized to all diabetics, occur after the onset of diabetes as a reaction to the individual's perception of the condition and to the physician and the clinical regimen imposed by him.

SUMMARY AND CONCLUSIONS

A review of the diabetic literature relating to per-

sonality and intelligence reveals studies which conclude that personality problems are generally associated with diabetes and those which report no unusual personality deviations in the diabetic.

Considerable conflicting evidence is also available regarding the intelligence of the diabetic. Studies have been cited which show lower than average intelligence as well as average and above average general intelligence. The present study was undertaken to lend some additional evidence to these problems.

The Minnesota Multiphasic Personality Inventory and the Stanford-Binet Test of Intelligence were administered to a sample of forty juvenile diabetics in the late adolescent and early adult age range. Although results showed some abnormal deviations when compared to the adult general population, these differences disappeared when the diabetics were compared to populations comparable in age. A general conclusion drawn is that with the MMPI as the measuring instrument, the juvenile diabetic is no more predisposed to behavior abnormalities than are normals. With regard to general intelligence, it is concluded that the diabetic I.Q. falls in the middle of the normal range. No relationship was found between diabetic onset age and abnormal behavior for any of the personality variables.

SUMMARIO IN INTERLINGUA

Le Personalitate e le Intelligentia de Diabeticos

Un revista del litteratura diabetic concernite con questiones de personalitate e intelligentia revela que il ha studios postulante como conclusion que problemas de personalitate es generalmente associate con diabete e altere studios que reporta que le diabetico exhibi nulle inusual deviationes de personalitate.

Le litteratura etiam revela considerabile conflictos del reportos relative al intelligentia del diabetico. Certe studios cita le conclusion que le intelligentia del diabetico es infra le nivello normal, secundo alteres illo es normal o supra le norma. Le presente studio esseva interprendite pro contribuer al clarification de iste problemas.

Le Multiphasic Inventario del Personalitate (Minnesota) e le Test Stanford-Binet de Intelligentia esseva administrate a quaranta juveniles diabetic de etates de adolescentia tarde e de adultessa primari. Ben que le resultatos exhibiva certe deviationes in comparation con le adulte population in general, iste differentias dispareva quando le diabeticos esseva comparate con gruppos de etate comparabile. Un del conclusiones general es que le Multiphasic Inventario del Personalitate non revela que le diabetico juvenil es in ulle maniera plus predisponite a anormalitates de comportamento que le nondiabetico juvenil. Quanto al question del intelligentia, le conclusion es que le Quotiente de Intelligentia del diabetico se trova al centro inter le limites del normalitate. Nulle relation esseva trovate inter le etate al tempore del declaration de diabete e anormalitates de comportamento manifeste in ulle del variabiles de personalitate.

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The Meaning of Body Weight

The gross body weight, *per se*, has some direct metabolic significance in that it affects the metabolic cost of physical activity. Most of the energy in physical activity is expended in simply moving the body around. With a fixed amount of activity—number, extent, speed and force of movements—energy expenditure tends to be directly proportional to gross body weight.[1] This not only affects calorie requirements; there is the integral need to provide digestion, respiration and circulation for this metabolism. In the unduly heavy person this could mean a strain on one or more vulnerable organs or functions. Such considerations could explain at least part of the excess mortality rate reported by insurance companies for overweight persons. But this argument amounts to concluding that total energy metabolism is a measure of biological strain conducive to illness and death. It suggests that persons with higher than average energy expenditures have an increased tendency to die early, regardless of the cause—increased body weight or increased amount of activity—of the high energy expenditure. Actually, however, it seems probable that many overweight persons are relatively inactive, physically, and do not have a particularly high total energy expenditure. Moreover, there is no evidence that sedentary persons are healthier and live longer than persons who are relatively active habitually. Only in the presence of abnormality or disease already established might it be suggested that reduction of the metabolic (and hence circulatory, etc.) load to a minimum is desirable.

From the book *Modern Nutrition in Health and Disease* edited by Michael G. Wohl, M.D., and Robert S. Goodhart, M.D., Philadelphia, Lea & Febiger, 1955, Chapter "Body Weight, Body Composition and Calorie Status" by Ancel Keys, Ph.D., p. 14.

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Changes in Serum Proteins and Polysaccharides in Rats with Uncontrolled Diabetes

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The etiology of diabetic glomerulosclerosis has been extensively investigated since Kimmelstiel and Wilson first described the lesions of intercapillary glomerulosclerosis.[1] These lesions have been shown to be characterized by hyaline deposits in the walls and lumen of the renal and retinal[2] arterioles and capillaries.[3] Although it was originally thought that this hyaline material was deposited secondary to degenerative changes in the vessel walls, more recent evidence suggests that such prior changes are not necessary. Dugild and Anderson[4] have demonstrated free clumps of mucopolysaccharide material in the lumen of vessels and have postulated that hyaline changes in diabetic arterioles and capillaries may occur as a primary phenomenon, secondary to abnormally high serum levels of mucopolysaccharide. In support of this concept, a number of investigators have described elevations of the a_2-fraction of the serum proteins, with which the largest fraction of a_2-globulin is associated.[5-10] Elevation of the a_2-glycoproteins has also been described.[11-16] However, elevation of the a_2-fraction of the serum globulins and protein-bound polysaccharides is not specific for diabetes, and has been described in a number of other diseases in which hyaline lesions of the small vessels are not observed.[17-21] It would seem, therefore, that a cofactor or predisposing abnormality of the arterioles and capillaries (other than degenerative changes) must exist in diabetic individuals. Lesions of the venules such as have been described by Ditzel and Sagild[22] leading to aggregation of red cells and a decreased rate of blood flow could result in an accumulation of hyaline material sufficient, in the face of increased serum glycoproteins, to form hyaline deposits. Another possible predisposing lesion might be capillary microaneurysms, shown by Friedenwald to occur in diabetic retinopathy.[23]

Although retinal and renal capillary lesions, containing mucopolysaccharide material, occur in a high percentage of human diabetics, they occur rarely, if at all, in the depancreatized or alloxan-diabetic rat. Only Foglia[24] and Mann[25] have described the occurrence of such lesions in the kidney of rats. Furthermore, the lesions described by them differ in two important respects from the pathology seen in the human. They are preceded by marked degeneration of the capillary walls and overgrowth of connective tissue is a prominent feature. Most investigators have found that diabetic rats, although developing cachexia, cataracts and ketosis, do not develop renal lesions comparable to arteriolar nephrosclerosis. It was decided therefore to study the levels of serum protein and protein-bound polysaccharides in rats with long-term uncontrolled diabetes in order to see whether changes similar to or different from those found in humans occurred in these animals, and if changes did occur, whether they occurred in the presence or absence of retinal and renal vascular lesions.

METHODS

Ten male, albino rats of the Charles River Strain, weighing from 225 to 280 gm. (10 to 12 weeks old) were fasted for 24 hours, and then given 45 mg./kg. of alloxan monohydrate intravenously. Two of the animals died within 24 hours of the injection of alloxan. The remaining eight rats were maintained on Purina Rat Checkers and water ad libitum. Since age alone might affect serum protein or polysaccharide constituents, six litter-mates were maintained under the same conditions. No insulin was administered at any time. Table 1 presents the weights and random blood sugars of the animals. Although the diabetic rats gained weight, this gain was much less than in the case of the normals;

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TABLE 1

Comparative weights and blood sugars in normal and diabetic rats

Rat No.	Date Injected / Initial Weight	10/18/54		11/1/54		11/27/54		12/28/54		1/21/55		2/25/55		4/6/55		Date Sacrificed (4/7-4/11) 55	
		Wgt.	B.S.	Wgt.	B.S.	Wgt.	B.S.	Wgt.	B.S.	Wgt.	B.S.	Wgt.	B.S.	Wgt.	B.S.	Wgt.	B.S. Fasted
1U	10/5/54		466		—		—		440		402		—		466		374
D	255	255		297		—		308		303		322		354		354	
2U	10/5/54		102		—		—		99		—		103		—		124
N	225	250		—		—		382		407		452		496		485	
4U	10/5/54		—		410		—		350		374		—		510		440
D	225	230		233		—		336		341		345		368		368	
7P	10/21/54		—		400		—		380		394		—		>600		400
D	286	—		293		—		407		377		392		385		380	
7U	10/21/54		—		380		—		380		318		—		432		264
D	275	—		275		—		374		317		345		345		343	
8P	10/5/54		440		—		—		380		266		—		456		304
D	264	284		309		—		407		372		404		406		390	
8U	10/24/55		—		—		—		394		304		—		>600		406
D	240	—		—		198		287		262		280		290		275	
9P	10/24/55		—		—		—		92		—		90		—		103
N	230	—		—		284		342		402		480		—		490	
10P	10/24/55		—		—		—		101		—		110		—		120
N	225	—		—		—		437		445		457		—		475	
10U	10/24/55		—		—		—		108		—		86		—		101
N	225	—		—		—		389		400		—		—		440	
12	10/24/55		—		—		—		114		—		112		—		94
N	224	—		—		—		500		507		511		—		493	
123	10/24/55		—		—		—		101		—		92		—		93
N	240	—		—		—		390		420		—		—		485	

variable but marked hyperglycemia was present at all times in the diabetic rats. In the twenty-third week, two of the surviving eight rats died and it was decided to terminate the experiment. Mann[25] described the presence of renal vascular lesions in 25 to 50 days in alloxan diabetic rats, with maximal involvement of the glomeruli within 3 to 6 months. Therefore, if such lesions were to occur, they should have had time to develop.

All of the rats were fasted for twenty hours prior to sacrifice. They were sacrificed in pairs on six successive days. Following nembutal anesthesis, they were exsanguinated from the abdominal aorta, using a silicone-treated syringe but no anticoagulant. Samples of muscle, liver, spleen, pancreas, thyroid, hypophysis and adrenals were taken for histological study. The aorta was removed in toto from its exit from the left auricle to its bifurcation into the two femoral arteries. It was split and placed in Bouin's solution. The eyes were removed by enucleation and placed in formalin. The tissues were examined after staining with hematoxylin and eosin. The formalin-fixed retinae were examined unstained in a drop of glycerin. In addition, the kidneys were exam-

ined after staining with periodic acid-Schiff, Bielschowsky's and trichrome.

The blood was allowed to clot, ringed, centrifuged, and the serum separated. The electrophoretic separation of the serum was started within four hours of the time of sacrifice. The sera of a diabetic and a control rat were run simultaneously for all six pairs—0.005 cc. of sera were applied across a section of a 4 cm. strip of S and S filter paper 2043A (0.04 cc. were used for carbohydrates). The apparatus used was a Pleuger type box, which carries twelve strips of filter paper on three racks. Two strips from the control animal and two strips from the diabetic animal were placed on each rack. The strips were run for 15 hours in a cold room at 4° C. Veronal-acetate buffer (*p*H 8.6, μ=0.1), and a potential of 150 volts and 15 to 19 ma. was used. The strips were stained for protein with Amido Black 10B. The periodic acid-Schiff reagent was used to stain for protein-bound carbohydrates by a modification of the method of Fraser.[26]

The protein strips were rendered translucent and read on a densitometer (Photovolt 525) using an orange filter (600 mμ). The polysaccharides were dried and read directly on the densitometer using a green filter (530 mμ). All strips were stained and read in duplicate. Values for duplicate strips agreed, with only a few exceptions, within 10 per cent.

Total protein in the serum was determined by the falling drop method.

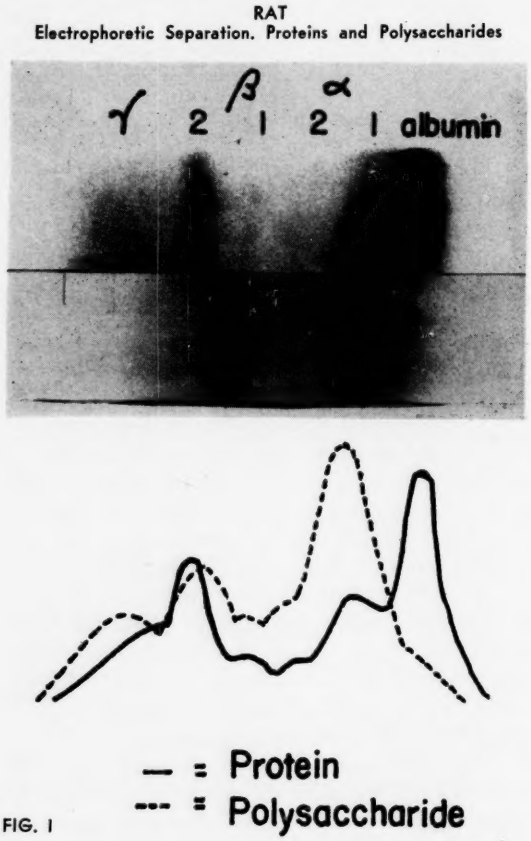

FIG. 1

RESULTS AND DISCUSSION

Microscopic examination of the tissues showed no pathologic changes in the renal or retinal vessels of the diabetic animals. Lesions of pyelonephritis, characterized by proliferation and scarring of the tubules, together with the infiltration of lymphocytes and mononuclear cells, were present in the kidneys of both the normal and diabetic rats and were of equal magnitude in the two groups. There was no evidence of atherosclerosis in the aortas. The islets of Langerhans were absent or scarce in the pancreases of the diabetic rats. The periodic acid-Schiff stain did not reveal any excess carbohydrate material in the glomerular vessels of the diabetic animals as compared with the normals. Some degree of "axial thickening" of the glomerular tuft, such as was described by Foglia[24] and Mann,[25] was present in the kidneys of both the normal and diabetic rats. No arterial or arteriolar lesions whatsoever were found.

Figure 1 shows the electrophoretic separation of serum proteins and polysaccharides in the rat. The top strip presents the proteins; the lower strip, the protein-bound polysaccharides. The densitometer curves, from which the amounts of the component proteins and polysaccharides are calculated, are shown below the strips. The serum protein of the rat contains, as in the human, five distinct globulin peaks: a_1- and a_2-, β_1- and β_2-, and γ. In the normal rat, albumin constitutes some 35 per cent of the total protein and the a_1-, β_2- and γ-globulins contain the major portion of the total globulin. Rat serum differs from human serum in having a lower albumin content and a greater content of a_1- than a_2-globulin.

Forty to 50 per cent of the total polysaccharides in the rat are bound to a_1-globulin. Another 20 to 25 per cent are present in association with β_2-globulin. Albumin binds only 5 per cent of the total polysaccharides, and the remaining 30 per cent are distributed in approximately equal amounts between a_1-, β_1, and γ-globulin. The total amount of protein-bound carbohydrate in the rat (as measured by planimeter areas) appears to be greater than in the human, and less is bound to a_2-

globulin. This may be secondary to the comparatively greater amount of a_1-globulin in rat serum.

Table 2 presents the individual data on the protein fractions in the two groups of rats, together with the means and standard deviations for each group. P was determined using Student's t test with Bessel's correction because of the small number of samples. With few exceptions, it can be seen that there was a high degree of reproducibility for the different components.

Total protein was reduced from 6.5 gm./100 ml. in the normal rats to 5.7 gm./100 ml. in the diabetic rats, while albumin concentrations fell from 2.28 gm./100 ml. in the normal to 1.99 gm./100 ml. in the experimental animals. Both of these changes are similar to those observed in humans, and are statistically significant. In the globulin fraction, the only statistically significant change occurred in the a_1-globulin fraction. The concentration of this fraction decreased from 1.10 gm./100 ml. to 0.79 gm./100 ml., or 28 per cent. This change is very different from the changes observed in human diabetics with renal or vascular disease. Here an increase in total globulins and, in particular, in a_2-globulin, is the most striking and consistent change described.[5, 7, 10] No significant changes in a_1-globulin have been described in human diabetics. The fall in the concentration of a_1-globulin in the rat is of particular interest in light of the work of Hoch-Ligeti and Irvine, who described a 40 per cent increase in the concentration of a_1-globulin in the serum of rats following the administration of a single dose of insulin (0.5 units).[27] It would appear from their work and our findings that insulin has a direct effect on the concentration of a_1-globulin in the rat. It also raises the question of the role of insulin in the changes described in the serum proteins of diabetic humans. At present, no data are available on the effect of insulin on the serum proteins in nondiabetic humans.

Table 3 presents the relative amounts of protein-bound carbohydrate found in the sera of the two groups of rats. Since no chemical determination of total protein-bound carbohydrate was carried out, no actual values other than planimeter areas can be given. The total planimeter areas in the diabetic rats are significantly lower than in the normal rats, indicating that the total amount of protein-bound carbohydrate is reduced in this group. The albumin fraction is small, shows marked individual variations, and is not significantly different in the two groups. There is a statistically significant fall in the amount of total globulin-bound polysaccharide, which is due almost entirely to the marked decrease in the amount of a_1-protein-bound polysaccharide. The mean planimeter area for this fraction was 4.1 in the normal rats and fell to 2.6 in the diabetic rats, a 37 per cent decrease. The amounts of a_2- and β-protein-bound polysaccharides appear to be slightly lower in the diabetic animals, but these changes are too small

TABLE 2

Serum proteins (gm. per 100 ml.)

Rat Number	Total protein	Albumin	Globulin	a 1	a 2	β 1	β 2	γ
				Normals				
123	5.6	2.30	3.30	0.99	0.35	0.33	0.77	0.88
10P	6.2	2.28	3.92	1.17	0.35	0.35	0.91	1.14
2U	6.6	2.04	4.56	1.12	0.40	0.40	1.27	1.37
12	6.4	1.68	4.72	0.94	0.39	0.45	1.07	1.88
10U	7.8	2.72	5.08	1.25	0.53	0.43	1.30	1.58
9P	6.1	2.63	3.47	1.16	0.35	0.29	0.83	0.84
Mean	6.5	2.28	4.18	1.10	0.40	0.38	1.02	1.28
S.D.	0.7	0.16	0.72	0.12	0.07	0.06	0.23	0.41
				Diabetics				
1U	5.6	1.87	3.73	0.71	0.36	0.36	0.91	1.39
7P	5.7	2.18	3.52	0.85	0.29	0.29	0.96	1.12
7U	5.7	1.96	3.74	0.79	0.43	0.43	0.93	1.12
4U	6.0	2.09	3.91	0.67	0.37	0.35	0.98	1.56
8U	6.2	2.00	4.20	1.07	0.48	0.42	1.17	1.07
8P	5.2	1.83	3.37	0.64	0.37	0.37	0.94	1.07
Mean	5.7	1.99	3.75	0.79	0.38	0.37	0.98	1.22
S.D.	0.4	0.13	0.29	0.16	0.07	0.05	0.10	0.21
P	<.05 >.02	<.01	<0.3 >0.2	<0.01	>0.5	>0.5	>0.5	>0.5

TABLE 3

Serum polysaccharides (planimeter area)

Rat Number	Total area	Albumin	Globulin	a 1	a 2	β 1	β 2	ν
				Normals				
123	7.9	0.4	7.5	3.5	1.0	0.7	1.7	0.6
10P	10.3	0.5	9.8	4.4	1.0	0.9	2.3	1.2
2U	11.4	0.7	10.7	4.4	1.3	1.2	2.6	1.2
12	10.9	0.4	10.5	3.7	1.1	1.1	3.1	1.5
10U	9.4	0.6	8.9	3.6	1.0	0.8	2.4	1.0
9P	10.4	0.6	9.8	4.7	1.1	1.0	1.8	1.2
Mean	10.0	0.5	9.5	4.1	1.1	0.95	2.3	1.1
S.D.	1.1	0.1	1.3	0.5	0.1	0.2	0.5	0.3
				Diabetics				
1U	8.3	0.3	8.0	3.1	1.0	0.8	2.1	1.0
7P	8.1	0.5	7.6	3.1	0.8	0.9	1.7	1.1
7U	7.0	0.6	6.4	2.1	0.8	0.9	1.7	0.9
4U	8.3	0.4	7.9	2.4	1.2	0.8	1.9	1.6
8U	8.1	1.0	7.1	2.2	1.1	1.0	2.0	0.7
8P	9.1	0.9	8.2	2.9	0.9	1.1	2.3	1.0
Mean	8.2	0.6	7.6	2.6	1.0	0.9	2.0	1.1
S.D.	0.7	0.3	0.7	0.5	0.2	0.1	0.1	0.3
P	<.01	<0.5>0.4	<0.01	<0.01	<0.3>0.2	>0.5	<0.3>0.2	>0.5

to be statistically significant. However, the percentile decrease in the various globulin-bound polysaccharide fractions is greater than the decrease in the corresponding protein fractions. This is shown in table 4, where the ratio of protein:polysaccharide moieties of the serum (derived from the per cent of the total amount of protein or stainable polysaccharide), is seen to be higher in both the *a*- and the β-globulin fractions. This suggests that the carbohydrate components of these compounds is actually lowered and that the decreases observed are not entirely secondary to decreases in available carbohydrate-binding protein. Despite the consistency of these increased ratios, the changes are too small to be definitive.

TABLE 4

Protein: Polysaccharide ratios in normal and diabetic rats

	Total	Albumin	Globulin	a 1	a 2	β 1	β 2	ν
Normal	0.65	4.6	0.44	0.27	0.36	0.40	0.44	1.2
Diabetic	0.70	3.3	0.49	0.30	0.38	0.41	0.49	1.1

These changes in the protein-bound carbohydrates of diabetic rats are opposite in direction to the changes observed in human diabetics with vascular complications. Gilliland and coworkers reported a rise in both the a_2- and β- protein-bound polysaccharides with the greater rise occurring in the a_2-fraction.[13] Berkman and his group,[12] Keiding and Tuller,[14] Neilsen and Poulsen[16] and many other workers have reported increases in the nonhexosamine, hexosamine, and mucoprotein fractions of the serum glycoproteins. Although some elevation of these substances has been reported to occur in diabetics without vascular complications[14, 16] other groups have found no such elevations.[12, 13] However, all of these investigators have confirmed a rise in protein-bound carbohydrates in the presence of diabetic arteriolar vascular disease, as exemplified by retinopathy and renal pathology.

It is apparent from these studies that the changes found in the serum globulins and globulin-bound polysaccharides of rats with diabetes without vascular complications are different from, and tend to be opposite in direction to, the changes found in humans with diabetes and vascular disease. Whereas both rats and humans develop a decrease in total serum protein and in serum albumin, humans develop increased amounts of a_2-globulin and total protein-bound carbohydrate. The major part of the increase in the total protein-bound carbohydrate is due to an increase in the a_2-fraction. Rats, on the other hand, exhibit decreased levels of a_1 serum globulin and total stainable protein-bound carbohydrate, the latter occurring because of a marked decrease in a_1-protein-bound carbohydrate. It is of interest, then, to speculate on the possible relationship of these opposite changes to the absence or presence of hyaline lesions in the vessels in diabetes. However, it must be borne in mind that

alloxan diabetes may not be analagous to diabetes as it occurs in man. If human diabetes is dependent on an endocrine imbalance above the level of the pancreas, then the production of hypoinsulinism alone may not initiate all of the pathology that occurs in the natural disorder. Also there are, as we have shown, certain differences between the composition of human and rat globulin and globulin-bound polysaccharide. Changes in the serum globulins and globulin-bound polysaccharides may not, therefore, be comparable in man and the rat. However, if these artefacts are not the reasons for the observed differences, it is possible that the fall in the a_1-globulin and the a_1-globulin-bound polysaccharide in diabetic rats may prevent the development of hyaline disease of the vascular system in this species, while elevation of a_2-globulin and a_2-globulin-bound polysaccharide may be responsible for vascular lesions in human diabetes.

SUMMARY

1. Changes in the serum proteins and protein-bound carbohydrates in rats with long-term uncontrolled diabetes have been studied.

2. The total serum protein and serum albumin are decreased in diabetic rats without vascular disease.

3. Serum a_1-globulin is significantly decreased in diabetic rats without vascular disease.

4. Total protein-bound polysaccharides are significantly reduced in diabetic rats without vascular disease. This reduction is due to a decreased amount of globulin-bound polysaccharide, particularly a_1-globulin-bound polysaccharide.

5. The relationship of these changes to changes found in the serum proteins and glycoproteins of human diabetics with vascular complications is discussed.

SUMMARIO IN INTERLINGUA

Alterationes del Proteinas e Polysaccharidos Seral in Rattos con Diabete Nontractate

1. Esseva studiate alterationes del proteinas e del hydratos de carbon ligate a proteinas in le sero de rattos con prolongate diabete nontractate.

2. Le total del proteina seral e del albumina seral es decrescite in rattos diabetic sin morbo vascular.

3. Globulina alpha del sero es significativemente reducite in rattos diabetic sin morbo vascular.

4. Le total de polysaccharidos ligate a proteina es significativemente reducite in rattos diabetic sin morbo vascular. Iste reduction es debite al reduction del polysaccharido ligate a globulina, specialmente globulina alpha.

5. Es discutite le relation de iste alterationes a alterationes trovate in le proteinas e glycoproteinas seral de diabeticos human con complicationes vascular.

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DISCUSSION

R. PALMER HOWARD, M.D., (*Oklahoma City, Oklahoma*): My question is whether there are similar changes in the rat in the polysaccharides with diabetes of any other kind except alloxan. Are there similar changes in other experimental animals in the polysaccharide distribution if different types of diabetes are produced?

It is hardly fair to compare diabetes in the rat with human diabetes.

ELIZABETH F. TULLER, M.D., (*Boston*): I think the question that Dr. Howard has raised is all too pertinent, both insofar as the method of producing diabetes in an animal is concerned as well as the difference, whether species difference or protein difference, in the effect that we saw.

To my knowledge—and some of the gentlemen here who have worked with the experimental lesions perhaps might wish to add anything more recent than I happen to know of their work—there has not been under any type of diabetes, whether natural or otherwise with one possible exception, a report of a lesion which every one is convinced is related to the full-blown clinically observed vascular lesions in the human.

It is certainly possible that the changes observed here might have been related to the fact that an alloxan diabetes is not a normal human diabetes. Since in any other method there has also been the problem of introducing these vascular lesions, and since with other animals we have run into similar contradictory effects, we have raised the question as to whether it is alloxan, the species or the proteins. We feel that there is something to be learned and to be thought about in terms of further work along these lines.

We did not ourselves run protein patterns on other types of experimentally produced diabetes.

Unstable Diabetes

Panel Discussion

Alexander Marble, M.D., Boston*
Moderator

Garfield G. Duncan, M.D.,† Philadelphia

George M. Guest, M.D.‡ Cincinnati

Robert L. Jackson, M.D.,§ Columbia, Missouri

E. Paul Sheridan, M. D.‖ Denver

MODERATOR MARBLE: Fortunately, most persons with diabetes have the condition in a form which is relatively stable. With anything like careful attention to diet, with an appropriate dose of almost any type of insulin and with reasonable constancy as to physical activity and attention to details of living, they get along very well, indeed, and pose no great problem to themselves or to their physicians. Furthermore, since the majority of these people have the onset of their diabetes in middle life or beyond, they have a good chance of living as long as, or even longer in many instances, with their diabetes than they might be expected, from life insurance tables, to live without it.

We are not concerned with that type of patient today. Rather, we are to discuss those patients who present a problem for all of us in everyday practice, namely those with unstable diabetes. These persons are sensitive to insulin and to physical exertion; they readily develop insulin reactions which are often severe and at times accompanied by convulsions; their blood sugar is sensitive to food or glucose as well as to infections or to emotional factors, and they have an easy tendency to ketoacidosis and coma. Fortunately, such patients are actually in the minority, although they loom large in our thinking because of the problems presented.

We have chosen today to speak of "unstable diabetes." We have discarded the term "brittle diabetes," because "brittle" suggests a quality of something that one can take in the hands, break in two, and then have two parts, with no resumption of continuity; this is obviously not the case in the situation we are to discuss. We recognize the terms "labile diabetes" and "insulin sensitive diabetes," as synonymous with unstable diabetes.

For the moment we will postpone discussion of those instances of what one might call spurious or iatrogenic unstable diabetes and concentrate first on the valid type. I would like to ask Dr. Guest to tell us his idea of the nature of unstable diabetes. Are we talking about diabetes that is unstable or about a diabetic person who is unstable? What is the influence of stressful situations and emotional factors in this problem?

DR. GUEST: Each member of our panel may offer a slightly different concept of what we here today call the unstable or brittle diabetic patient. I shall of course confine my discussion to diabetes in children.*

Let us note first that all juvenile diabetic patients are more or less unstable with regard to their changing needs for insulin. With changes in physical activity and with brief intercurrent infections their insulin require-

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ments are apt to vary widely, sometimes abruptly. Let us note also that even the nondiabetic child, compared with an adult, has greater diurnal fluctuations in blood sugar and is more prone to develop ketosis following short periods of fasting. This is presumably due to narrower margins of glycogen stored in the liver and generally higher metabolic rates in proportion to body weight.

The term "unstable" is usually applied to those patients in whom the adjustment of insulin dosage for proper control is more difficult than in other patients of the same age who receive approximately similar instructions with regard to diet and to indications for insulin dosage. Such patients from time to time are apt to show unusual sensitivity to insulin, with hypoglycemic reactions difficult to predict; and they are also prone to develop ketosis quickly with seemingly only slight deficits of insulin.

The most striking examples of extreme instability, with difficulties in diabetic control, are found among those children who have developed the so-called Mauriac syndrome, with a triad of symptoms of dwarfism, hepatomegaly and mild obesity (discussed in an editorial in DIABETES 2:415-17, Sept.-Oct., 1953). In this syndrome one sees evidence of multiple interrelated but more or less separate metabolic derangements that may accompany the diabetic trait, with varying manifestations in different individuals. In children of small stature, the "diabetic dwarfs," both growth failure and hypersensitivity to quick-acting insulin may be associated with pituitary deficiency. The hepatomegaly that develops in these children conceivably may be brought about by alternating states of hyper- and hypoinsulinism, as the livers have been found surcharged with glycogen or fat or both. Some authors suggest that a defect of glycogen metabolism similar to that observed in glycogen-storage disease may coexist with diabetes mellitus in the young diabetic with this syndrome; if so, this metabolic fault in the turnover of glycogen could be related both to their sensitivity to quick-acting insulin and to their tendency to develop ketosis easily. The pseudo-obesity with moon face has been thought to be related to excessive liberation of corticosteroid hormones by overstimulation of the adrenal glands during alternating periods of hypoglycemic reactions and of ketosis with insulin insufficiency. Dr. Janet McArthur has demonstrated increased urinary corticosteroid excretion in a young diabetic both when ketosis was induced experimentally by withholding insulin, and when hypoglycemia was induced by slightly larger than needed doses of insulin. Thus there is reason to believe that wide and abrupt fluctuations between hyper- and hypoglycemia, and periodic development of ketosis, constitute situations of stress with attendant mutually aggravating metabolic derangements that have far-reaching deleterious consequences.

We have observed this syndrome in a number of children at two to five years of age who were referred to our clinic with histories of difficulty in their diabetic control. When they were treated according to our practice, with normal unmeasured diet and slow-acting insulin administered in dosage adjusted to permit continuous mild glycosuria they promptly improved in growth pattern and their enlarged livers receded to normal size. This type of unstable diabetic child is, I believe, much better off if allowed to have continuously an even level of mild hyperglycemia and glycosuria than if one attempts to maintain an aglycosuric state.

Dr. Marble asked me to comment on the significance and possible dangers of repeated episodes of hypoglycemia in these "unstable" diabetic patients. I should like to call attention to an excellent concise editorial in the British journal, *Lancet,* May 5, 1956, page 618, on "Hypoglycaemia in Diabetics." After citing various causes of hypoglycemia, the editor emphasized the importance of hypoglycemic encephalopathy and susceptibility of the brain to "what may be irreversible damage," caused by repeated hypoglycemic episodes. The encephalopathy that develops after severe hypoglycemic episodes may involve subsequent late complications associated with histologic changes in the brain and functional deterioration demonstrable by electro-encephalography and psychometric tests. The editor states: "This is certainly a danger to be weighed against the advantages that can be attributed to long-term strict diabetic control . . ."

The permissive so-called "free-diet-glycosuric regimen" followed in our clinic in Cincinnati is one of which my colleagues on the panel do not thoroughly approve, but it does offer a margin of safety which I believe is an important protection against the potential dangers of frequent hypoglycemia—especially in the "unstable" young diabetic child.

MODERATOR MARBLE: Thank you, Dr. Guest. Dr. Jackson, would you like to comment on some of the remarks of Dr. Guest?

DR. JACKSON: Yes, I have been silent all morning and have been looking forward to an opportunity to make some comments. As most of you know, this is no new experience for Dr. Guest and me. We have done this many times and we realize that we are getting closer to the truth by honest exchange of ideas.

I agree that with very few exceptions the child with diabetes belongs to the group of so-called unstable diabetics. Most, if not all, children with diabetes require multiple daily injections of insulin if glycosuria and insulin reactions are to be avoided. I would like first of all to discuss the insulin requirements of children and point out that there is a rather uniform pattern despite the fact that the requirements are changing in relationship to the growth of the child. The changing insulin requirements can be understood only when they are related to the growth of the child. Prior to insulin therapy, the child with diabetes depletes his nutritional store; thus, during the initial phase of management, he rebuilds his body tissues and stores to normal. During this time his requirement for insulin and food are higher than the maintenance requirement. We also have observed, as Dr. Priscilla White stated this morning, that the insulin need for the size and age of the patient was low (approximately 0.2—0.3 units/pound/day) for a period of months after initial regulation and metabolic restoration. Then the requirement increases gradually until it reaches the range found for the group of diabetic children of the same age and size. The amount of insulin required and the duration of the period of metabolic recovery depend on how long the state of hypoinsulinism and catabolism have persisted. After stabilization is achieved, the insulin requirement becomes fairly constant (approximately 0.4—0.5 units/pound/day) if the food intake is adequate and adjusted to compensate for variations in physical activity. During the early period of treatment, the weight of the child increases rapidly, but height remains almost stationary. However, within a short period (two to four months), the child's height begins to accelerate, and concurrently with this increase in growth rate, the insulin requirement increases and eventually attains in general almost a constant ratio with body weight. Up to ten years, the growth patterns of the boys and girls are quite similar, in contrast to the great difference after ten years. The insulin requirement reflects the period of similarity and differences in the sexes and clearly shows a relationship of insulin requirement to growth. One observes a smooth rise of insulin requirement in harmony with the fairly uniform growth in the mid-childhood period. The insulin requirement of girls increases rapidly after ten years, concomitantly with their prepubescent growth spurt, and decreases after the period of rapid growth. The insulin requirement of boys increases rapidly after twelve years, concomitantly with their prepubescent growth spurt, and decreases gradually as adulthood is reached. The rate of change in insulin requirement is dependent on whether or not the disease has its onset in mid-childhood or just prior to or concurrently with the prepubescent growth spurt, being accentuated during this period of rapid growth. It is very important to know and to be able to predict the future insulin requirements of a given child, to allay the fears on the part of the child and the parents who may assume that the disease is growing worse if the insulin requirement is increasing.

I also would like to comment in regard to damage of the central nervous system. There is no question but that very severe or frequent and severe insulin reactions can cause irreparable damage to the central nervous system. When this occurs, we have a very unstable, brain-damaged diabetic child. The point I would like to stress is that severe insulin reactions can be avoided provided the insulin given is distributed properly. This was emphasized by Dr. White this morning and I would like to talk about this again later. It also is true that the child who has had a period of poor control for over six months to a year—and it will depend on the degree of control—becomes progressively more difficult to regulate. Under these circumstances it becomes practically impossible to maintain good control. Control does become a very serious and practical consideration and in these children it then becomes necessary to permit varying degrees of glycosuria to avoid insulin reactions. It is important, therefore, to attain and maintain a high degree of control to prevent so-called unstable diabetes in childhood from becoming more unstable.

This brings us back to the important question raised by Dr. Ricketts this morning as to what is meant by good control. According to my standards, a patient is in good control when repeated daily urine specimens are free from sugar except for occasional minimal amounts, blood sugar values obtained periodically are normal or only slightly elevated, and there are only very occasional mild insulin reactions.

MODERATOR MARBLE: Thank you. I fear, however, that up to this point we have left the impression with the audience that serious brain damage from hypoglycemia is an ever-present possibility and of frequent occurrence. Dr. Jackson, is such really the case if one takes reasonable care as to selection of insulin dosage?

DR. JACKSON: What I am trying to say, and apparently didn't do a very good job, is that if the child's diabetes is recognized early and adequate management is undertaken initially, it is practicable to attain and maintain essentially complete control of the disease.

The juvenile patients with the most unstable diabetes are those who have had improper management either from having severe insulin reactions resulting in brain damage or patients who have been allowed to be glycosuric for prolonged periods of time. These are the severely difficult juvenile diabetic patients who are the result of improper treatment.

MODERATOR MARBLE: Lest we not have a good opportunity to mention it later, Dr. Jackson, I would like to ask you now one more question. Would you care to comment on the difficulty and possible confusion in diagnosis between seizures of hypoglycemia and those due to epilepsy? What are the means of differentiation and treatment?

DR. JACKSON: This is a very practical question but difficult to answer. An accurate detailed history is of most help and blood sugar determinations at the time of the convulsion also are indicated. We have made serial electro-encephalograms from a large number of children with diabetes at the University of Iowa. I am sorry that with my leaving the University of Iowa, these data have not been entirely evaluated, and, therefore, I am hesitant to say much about them. One thing is certain, and that is that with severe and repeated insulin reactions definite changes in the electro-encephalogram appear. These patients many times are benefited by the use of anticonvulsant drugs. These children have attacks with varying levels and shifts in blood sugar values. The differentiation is extremely difficult and many times a therapeutic trial is desirable and is the procedure of choice.

We have made electro-encephalograms on many diabetic children prior to instituting insulin therapy. The frequency of abnormal tracings is higher in this group than in normal children without a history of convulsions. The tracings from some of the diabetic children reverted to normal after their clinical status improved with treatment. This suggests that some of the abnormal tracings are related to the abnormal metabolic state. Dr. John McQueen, of the University of Iowa, is analyzing these data and I hope the results will be published soon.

MODERATOR MARBLE: Thank you very much. Next I would like to turn to Dr. Sheridan and ask him when an unstable diabetic is not an unstable diabetic!

DR. SHERIDAN: To answer this question will be quite difficult. First, let us consider the unstable diabetic as an emotional problem. I feel quite strongly that, with the adult group of patients, various tension states and psychological adjustments will revert a controlled patient into one that may show the wide fluctuations of glycemia so common in the labile group. The "unstable diabetic" may also be one that is well adjusted emotionally and in this patient his diabetes may be a most difficult problem. Thus, in the emotionally unstable group the utilization of various sedatives or tranquilizing drugs may help; in the latter group various changes in diet, readjustment of insulin dosage should prove effective. A very important, but often forgotten fact, is the help derived from a sympathetic and understanding physician.

MODERATOR MARBLE: Dr. Sheridan, I wish you would discuss the problem a little further, if you will, please. What are some of the confusing factors which may cause the physician to regard the patient as one difficult to treat?

DR. SHERIDAN: I think the following problems should be given consideration in the management of the unstable diabetic:

(1) Chronic lung disease with particular emphasis on the prompt recognition of early tuberculosis. Therefore, frequent chest films are needed and especially in the patients who begin to show characteristics of uncontrolled diabetes.

(2) Thyrotoxicosis must be considered in the unstable diabetic. We find the I^{131} uptake and PBI determinations to be helpful in such states. A minimal degree of hyperthyroidism may shift a patient into this difficult group.

(3) Chronic pyelonephritis, especially in the female diabetic patient, should be evaluated and if such a focus of infection is found, it must be treated vigorously and observed over a long period of time.

(4) The improper administration of insulin perhaps is superfluous but must be considered. One should carefully search for "insulin pads" and insist that the patient rotate his injection sites in orderly fashion to assure proper absorption of insulin.

MODERATOR MARBLE: So far, we have been skirting the edge of this problem a little bit. I think it is time to come to closer grips with it. Patients with the most unstable diabetes often travel from clinic to clinic, from doctor to doctor, if they are sufficiently well off financially, and pose a problem for each group. I am sure that over the years, Dr. Duncan has seen many, many patients of this type. We would all benefit by having him give us a rundown on his views as to the management of the patient with unstable diabetes. Dr. Duncan.

DR. DUNCAN: There are certain advantages in being the last member of the panel to be called on to speak because one collects ammunition along the way. I would like, before answering the question Dr. Marble posed

to me, to correct a couple of misconceptions that might have crept into this discussion.

I think that to abandon the advantages of good treatment as a means of preventing neurologic complications of hypoglycemic reactions might be justified *if* we couldn't prevent these disorders in a more practical way. To permit poor control of diabetes as an excuse for failure to apply advantages at hand is, I think, entirely wrong. Furthermore, neurologic complications of the type mentioned are rare, in Philadelphia at least, and they occur not as the result of frequent transient hypoglycemic reactions, but from severe prolonged hypoglycemic reactions, and why I am not seeing them in my practice probably is because I have all but abandoned the use of protamine zinc insulin which when not used to best advantage is prone to cause hypoglycemic reactions during the night. Frankly, I think it should be taken off the market! It has served a good purpose but with appropriate selection and use of the other insulins on the market, nothing would be lost without it.

Now to return to do as I am asked to do concerning the management of these patients—I won't embark on the difficulties involved more than to say that a higher degree of individualization is necessary in dealing with these patients than with almost any other type of patient. They must be given time. These patients, most of them, are emotionally unstable and if they get the impression one is in a hurry, the door to obtaining their confidence is closed. To get their confidence is essential to best results. In the sympathetic understanding of their problems one may get valuable information about home situations. A complete psychiatric history should be secured. This should be by the internist, not by the psychiatrist—that is fundamental. I think, for instance, the diabetic patient will think it quite silly to be asked: Do you think that you enjoyed nursing at your mother's breast? Equanimity will prevail and time will be spent to better advantage if one gets down to problems at hand.

The home situation is important. For instance, many husbands, let us say, particularly of Italian descent, dislike slim wives, and if one wants to reduce the obese, diabetic Italian woman, he must cope with her husband and to bring him into line is not always easily done. The home situation should be gone into in detail. Under this type of encouragement, patients may come up with the most diabolic stories stemming from their experiences with other clinics. A good way to disarm these patients, after they report something that is obviously ridiculous, is to say, "Most remarkable, Madam; most remarkable" and then proceed according to plan!

The young person of teen age, with unstable diabetes, which is upset still further by anxiety, may be concerned about the question of marriage and of having children. Reassurance along those lines might come along, not necessarily in the first visit, but later on.

The real restriction in their activities is that they should observe uniformity in diet and exercise from day to day. I might *almost* agree with the free diet enterprise if such a diet were uniform from day to day. It would then be possible to control the diabetes more satisfactorily. But, of course, you can't do that with the free diet as it is employed today.

Patients with unstable diabetes, in particular, need an initial period of hospitalization. They gain confidence and their physician gets to know them better. They get to know their physician. He observes their responses to therapy and greater opportunity for instruction is permitted. It is a good plan to give each patient a list of the various things a diabetic should know and be sure that they do know them before they leave the hospital.

It is important, too, for them to have erroneous ideas about insulin corrected such as the statement that if they once start taking insulin, they may never be able to drop it. Unfortunately, this is usually true with this group of patients, but nevertheless, they can be encouraged by knowing of the number of patients who may have the dosage of insulin reduced, the number of doses reduced, and in knowing that a considerable number of patients are able to omit insulin.

The diet should be adequate and it should be suitably divided. We like to divide it, for these patients with unstable diabetes, into three equal meals and then take a bread and milk exchange from breakfast to be consumed at 11 a.m. A similar amount is taken from lunch for a 4 p.m. snack and a like amount from supper to be eaten at bedtime. You may say that is inconvenient. Well, most of us have coffee breaks at 11, it is a good British custom to have afternoon tea and many persons like to eat at bedtime. Combined, these features provide a good program for these patients.

In selecting the insulin or insulins, it is to be borne in mind that most of these patients do not do well with a single dose of a single insulin daily. Usually none of the intermediate acting insulins will act quickly enough to achieve good control of the diabetes during the forenoon. For most of these patients we select NPH insulin because when mixed with regular insulin, the result is, I believe, more predictable than when either of the other intermediate acting insulins is used. We

add regular insulin to it to control the diabetes during the forenoon. The NPH insulin takes over in the afternoon and evening and then a small dose of NPH after supper provides smooth control of the diabetes throughout the night. With the advantages we have in these insulins, the proper selections, the proper combinations and timing of the administrations, and with the proper prescription and appropriate distribution of the diet, I see no excuse for advocating poor control of the diabetes. At best, the control won't be perfect. With this I agree, but to advocate poor control of the diabetes while excellent resources go unused, I think, is wrong.

MODERATOR MARBLE: Thank you, Dr. Duncan. I would like to take a little exception to one of Dr. Duncan's statements. He mentioned the dangers of protamine zinc insulin. We use protamine zinc insulin very little now, and usually start no new patients on it. I believe, however, that protamine zinc insulin can be used successfully if one pays attention to its activity time and realizes that one must not exceed that dose which will give a normal or close to normal blood sugar twenty-four hours away from the time of its injection. In actual practice one usually needs to supplement it with appropriate doses of crystalline insulin.

I would like to mention one other point regarding the free diet. If the free diet means the inclusion of straight sweets, pastry and other foods with sugar in readily absorbable form, the time required for digestion is almost nil and the rate of absorption is very swift. In the patient about whom we are talking now, in whom there is little or no native insulin and little or no islet tissue to stimulate, the effect of straight sweets and pastries may be so overwhelming and so rapid that injected insulin cannot possibly be expected to cope with it. That would be my chief objection to the absolutely free diet.

I think that Dr. Sheridan has some ideas regarding the adjustment and spacing of food. Would you care to comment further, Dr. Sheridan?

DR. SHERIDAN: The diet must be given the number one spot in the control of such patients. I feel that it is wise, at least during the initial adjustment period, to lower the carbohydrate content, and the protein content should be quite high. As better control is achieved, the carbohydrate intake can gradually be raised. A diet properly spaced will prove effective in many such cases. Our plan has been to divide the feedings into four equal parts and give such meals at seven, twelve, five and bedtime. Such diet changes will fit the so-called split insulin dosage technic quite well. I feel that if the unstable patient can be controlled, the wide fluctuations in blood sugar values will decrease and the patient may revert to his original diabetic pattern.

MODERATOR MARBLE: In our panel there are apparently four to one against Dr. Guest, so it is only fair to let him have another opportunity to give his side of the advantages of a more liberal regime.

DR. GUEST: Delighted. I would reply to Dr. Duncan that there is need for better definitions of our terms, especially with regard to what constitutes "poor control." Let me recall that Dr. Marble and I once debated the pros and cons on the controversial subject of the so-called free diet in the editorial pages of DIABETES 1:487-89, 1952. There I pointed out that the proponents of the liberal regimen do not condone carelessness or reckless excesses in eating habits. Actually, differences of opinion among members of our panel regarding the essential desiderata for control are mainly confined to the amounts of glycosuria deemed permissible. All agree that the diet should be a sensible "normal" one, whether it be measured or unmeasured. Under our permissive regimen we adjust the insulin dosage to permit almost continuous mild glycosuria. There is abundant evidence, both from clinical experience and from experimental metabolic studies on animals, that good growth with positive metabolic balances of minerals and nitrogen and other nutrients can be sustained despite a considerable degree of glycosuria if the dosage of insulin is adjusted adequately to prevent the appearance of ketonuria.

In our Cincinnati Clinic there are two children who developed diabetes in infancy, one at three months and the other at nine days of age, who are now respectively 11 and 9½ years of age. They have shown normal growth and development and they have never been hospitalized for any crisis either of acidosis or of hypoglycemic shock. Their present daily insulin dosage of 35 to 40 units (Globin insulin) corresponds to the average for that age reported by Dr. Jackson. I regard these two children as having been well controlled despite considerable degrees of glycosuria indicated in most of their daily records. Apart from their mother's excellent supervision, the boys themselves are alert to signs of trouble and quite capable of good daily self-management, with adjustment of insulin dosage according to changing needs indicated by the daily urine tests. For them the appearance of ketonuria is the most important single sign of impending trouble, which may be experienced during respiratory infections or other illnesses. Let me add that these boys never presented problems of "unstable diabetes," the main subject of our panel.

Dr. Marble has passed to me the following question: How do you measure pituitary function, when investigating the possibility of pituitary insufficiency?

My speculations on the possible role of pituitary insufficiency in the diabetic dwarf were based only on indirect evidence, not on any personal laboratory study (see the editorial in DIABETES, already cited, on the Mauriac syndrome).

MODERATOR MARBLE: Thank you. In my experience one of the commonest errors in the field of regulation of the unstable diabetic is to fail to recognize that not all persons with diabetes respond to a given variety of insulin in the same way.

When one says that NPH insulin or Lente insulin is effective for twenty-four or twenty-six hours, one simply means that in most diabetic patients this is the case. I think all of us have come over the years to find that there are a good many exceptions, and in many cases these varieties of insulin, good though they are and perhaps the best that we have at the present time, begin to lose their effect some 18, 20, or 22 hours after injection. Thus, although the diabetes may be well controlled during the course of the day, there is a rise in blood sugar in the early morning hours to high fasting levels. That may not be reflected in the urine test because the specimen examined may represent a composite of urine collected in the bladder during the entire night. One may find even a sugar-free test, and yet a fasting blood sugar of 200-300 mg. per cent. One must suit the insulin dosage and distribution to the individual concerned. One of the persons in the country who over many years has done that with great skill has been Dr. Jackson. I wonder if he would give us a brief discussion as to his present practice.

DR. JACKSON: I heartily agree with everything that Dr. Duncan has said including discontinuance of protamine zinc insulin on the market. I wrote the first paper on the dangers of protamine zinc insulin a few years after its introduction.

I would like to stress one thing of which I am sure everyone is aware, but it needs to be emphasized. That is the tremendous importance of varying food intake with varying physical activity. In terms of dietary management I have been using essentially a free diet for many years. That may sound very surprising to many of you, but it is true. In fact, the differences in dietary management between Dr. Guest's regimen and mine are minimal. We both have attempted to provide the children a normal diet in keeping with their growth requirements and family eating pattern. The major difference in the two regimens is the distribution of insulin and the control of glycosuria. What I do is what Dr. Marble advised and that is to adjust the kind of insulin and the distribution of it to maintain good control insofar as possible. This can be done with a great degree of success by giving multiple doses of insulin.

In this regard I would like to say we still use three injections of insulin daily for the initial regulation of the patient and for the initial instruction of the parents. Regular insulin is given before the early morning meal and again before the noon meal, and an intermediate type of insulin such as globin or NPH is given before the evening meal. This is very desirable so the parents will be familiar with a method of control using regular insulin for the management of intercurrent infections. Frequent adjustment of the insulin doses is desirable during stress situations to avoid ketosis and the possibility of re-hospitalization of the child. It is now possible as reported in the January 1956 issue of DIABETES, to maintain satisfactory regulation of juvenile diabetes in approximately 90 per cent of cases, using a two injection program, a mixture of globin or NPH and regular insulin in the morning and globin or NPH insulin in the evening. Approximately two-thirds of the total dose is given before breakfast using a two to one mixture of globin or NPH and regular insulin and the remaining one-third of the total dose is given as globin or NPH one hour before the evening meal.

DR. GUEST: I should like to disagree with the unfavorable opinion both Dr. Duncan and Dr. Jackson expressed regarding protamine zinc insulin, because I have found it most satisfactory in many cases, when used judiciously. Let us recall Dr. Marble's excellent review on hepatomegaly in diabetic children (*Arch. Int. Med.* 62:740, Nov. 1938), in which he stated that the high incidence of hepatomegaly observed prior to the introduction of protamine zinc insulin decreased sharply after the slow-acting PZI came into use. In certain cases I still prefer to use improvised mixtures of PZI and regular insulin in proportions varied according to need as judged by the patient's own urine-testing.

MODERATOR MARBLE: Thank you. I think one of the errors that all of us have fallen into over the years is the attempt to make treatment too convenient. The aim is laudable but when it results in poor control of diabetes, it should be abandoned. It is our practice now, and we think it is quite successful in many patients with unstable diabetes, to give in the morning before breakfast a dose of NPH or Lente insulin with or without a dose of crystalline insulin and a second dose of NPH and Lente insulin either before the evening

meal or very often at bedtime. The bedtime dose is accepted by most patients more willingly than one before the evening meal, but the main point, however one arranges it, is to recognize the need in many patients of more than a single dose of insulin a day.

Dr. Jackson, just one question from the floor here before we let you go. How frequently do you observe clinical evidence of encephalopathy or of deterioration of the intelligence in children who experience many insulin reactions of varying degrees of severity, some requiring intravenous glucose in therapy? Can you answer that in a word or two?

DR. JACKSON: As in Philadelphia, we see this very infrequently, but this should never occur and it is tragic when it does. Most of the patients we have seen have, as described by Dr. Duncan, a history of severe prolonged periods of hypoglycemia associated with convulsions. These children have irreparable central nervous system damage and with very few exceptions these brain-damaged children have a poor prognosis.

The other thing that we had to learn from experience was the importance of increasing food intake to compensate for increases in physical activity in order to avoid even minor insulin reactions. This is very important for the emotional well-being of the patient.

MODERATOR MARBLE: One other question from the floor is addressed to Dr. Jackson. What mechanism is responsible for the development of hard-to-manage, unstable diabetes after six months or more of poorly controlled juvenile diabetes?

DR. JACKSON: Thank you, Dr. Marble, but I am unable to answer this question. The insulin requirement of this group is not significantly different from the group treated adequately shortly after onset. Therefore, I do not believe it is due to a difference in availability of endogenous insulin.

MODERATOR MARBLE: Without encroaching on the field of another portion of this program, I would like to ask Dr. Duncan whether treatment with sulfonylurea compounds, that is to say, BZ-55, or Orinase, has any effect on the "stability-status" of unstable diabetes. That is, can these preparations make diabetes more or less stable?

DR. DUNCAN: Our experience with these compounds is not great nor of long duration, but with these compounds in general, my answer to Dr. Marble's question is—patients having unstable diabetes apparently receive least, if any, beneft from these preparations. But there are exceptions.

I have one patient, in particular, who is quite resistant to insulin, and she has a relatively unstable diabetes. She was taking from 160 to 180 units of insulin and was in trouble off and on. She was given carbutamide (BZ-55) and later changed to tolbutamide (Orinase). The outcome was the same with each of these drugs. She was able to reduce her daily dosage of insulin to 80 units achieving at the same time a much greater stability of her diabetes. This patient is much older, being in her seventies, than most members of the group under discussion.

I have observed only three patients like this one. These are exceptions, I believe. The patient with unstable diabetes cannot look forward to much, if any, benefit from the sulfonylurea compounds that are available at the present time.

DR. JACKSON: Dr. Duncan, how can you be sure that the closer management was not responsible for the improvement of these patients rather than the drugs?

DR. DUNCAN: You mean in the one patient that I referred to?

DR. JACKSON: The one or three that were the exceptions. I assume all of them are getting this individualized care that you stressed which I think is most important.

DR. DUNCAN: To answer this question I should state that none of these three patients had ever been overweight. They are all adults and have been under observation for from 4 to 20 years. This is no transitory affair. It is real. Within the past year each of these patients was observed in the hospital. In studying the effects of the sulfonylurea compounds, the dosage of insulin was reduced sufficiently, in each case, to permit a considerable degree of glycosuria which was measured daily for five days. In each of the succeeding five days each patient was given 2 gm. of one or the other of the two sulfonylurea compounds currently available. During a third five-day period, the drug was withdrawn. In each of these three exceptions, the glycosuria was significantly less while taking tolbutamide or carbutamide than it was during the control periods, one before and one after their administration. I consider these results as proof of the effectiveness of these remedies in controlling glycosuria and in reducing the level of the blood sugar in these three patients.

MODERATOR MARBLE: Thank you, Dr. Duncan. I hope that as a result of this panel today we have convinced the audience that this is an important problem and second, that some of the patients with so-called unstable diabetes really have a condition which is not as unstable as first might seem but the apparent instability may be caused in part by the type of treatment imposed. Third, that if one individualizes treatment and

is careful about the regulation of diet, the time of administration of food and the selection of the type of insulin and its distribution throughout the day, and if one attempts to secure relative constancy of physical effort, one may achieve a high measure of success even in the patients with the most unstable form of diabetes. Finally, I think that regardless of our differences of opinion as to the type of diet and the degree of regulation of glycosuria and hyperglycemia to be sought, we all hope to restore conditions to as nearly normal as we can without provoking frequent and severe insulin reactions and making life intolerable for the patient. We hope that with attention to details of treatment, one's efforts may be rewarded over the years by a lessened incidence of complications and a longer, more useful life. Thank you all for attending today. I wish also to express my appreciation to the members of the panel for their excellent discussions.

Food Faddism and the Consumer

Myths, magic and superstition are as old as the history of man. Food fads are not new, but the forms they take vary from month to month and from year to year. In 1908, C. Stanford Read, a physician, published *Fads and Feeding* (London: Methuen, 1908). Apparently, the problem was of great enough concern in London to warrant the publication of a book about fads. The first paragraph of the preface reads very much as though it might have been written in 1954 rather than in 1908, before the word "vitamin" had found its way into medical and lay literature.

"Modern civilization seems to bring many undesirable factors with it, and one which stands out prominently is the 'fad' which has crept into every department in our daily life. Medicine has of late made great advances, especially on its 'preventive' side, but where most physicians fear to tread, some well-meaning individual steps forward and unauthoritatively and unscientifically shows the public that for centuries they have been courting disaster by swallowing the wrong food. It is undoubtedly right that we should all be, to some extent, upon our guard concerning what we put into our interiors; yet this introspection can be carried too far until it becomes morbid, and by its means we may bring about the very result we wish to avoid."

The author was concerned about the amount and type of dietetic information published in that day, even as we have serious concern today:

"Since the lay press has been so multiplied and extended, and has become such a power in the land, many self-appointed authorities, by means of the columns of newspapers and magazines, think fit to dogmatize on some particular dietary or to rail against the pernicious effects of certain foods. Doubtless many, though unscientific and illogical, are sincere in their intentions; yet many others, I fear, recognize that their peculiar views and dogmatism will bring them kudos and pecuniary compensation, which is the real aim they seek. The more extreme a faddist proclaims himself, the more converts rally beneath his standard: and for the sake of novelty, for the sake of belonging to an elect cult, there seems to be an ever-increasing number of individuals who for a time, at least, will believe any fresh dietetic rubbish that comes under their notice."

Because so much progress has been made in the understanding of food and its relation to health, the field of nutrition offers fertile soil for those who wish to exploit half-truths and misinformation for their own profit. It appears that there is a rapidly growing segment of our population whose chief purpose is to secure attention and financial security by whatever method seems most feasible at each stage in the advancement of the science of nutrition.

How can we best help the confused consumer? Serious efforts have been and are now being made to help the public determine for themselves a sane and sensible road to good nutrition. It would be easy, but not realistic, to lay all responsibility for nutrition education in the hands of those who teach our youngsters, and sit back quietly and wait for a generation of children to develop into adults for whom fads and quackery might have no appeal. It is likely, however, that the vast majority of teachers do not have an understanding of the basic concepts of nutrition, for thousands of potential teachers are graduated each year from our colleges and universities without having had the opportunity to acquire this information. Consequently, we cannot hope for useful nutrition education in all of our schools until our institutions of higher learning recognize the need for nutrition education during teacher training.

From the School of Public Health, University of Michigan, Ann Arbor, by Adelia M. Beeuwkes, in *Federation Proceedings* 13:785-89, September 1954.

Rare Clinical Manifestations in Diabetic Coma and Precoma

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The classical picture of diabetic coma is properly looked upon as a flaccid, muscularly relaxed and totally unconscious state in which only the breathing muscles, driven to air-hunger, are obviously active. However, over many years I have noticed some exceptional features unrecorded in detail anywhere and although some have been briefly cited, (Lawrence[1]) they are not included even in Joslin's voluminous classic. To describe them may help in the assessment of these unusual happenings which may confuse the diagnostic issue and perturb the physician.

MANIACAL RESTLESSNESS AND VIOLENCE

I have seen this condition some fifteen times but can not say what percentage of total cases of coma this represents.

The first patient, a strong diabetic boy of sixteen, was very puzzling to me in 1928. There was no doubt of his intensely diabetic state, his insulin having been criminally stopped for two days on account of vomiting. On his arrival in flaccid coma his blood sugar was 870 mg. per cent and the room stank of acetone. One hundred units of insulin were given subcutaneously. During these procedures he became so violent, especially when touched but also without this stimulus, that further treatment was a terrible struggle and I was unable to establish the saline intravenous infusion which was then in use in severe dehydration.[2] In despair I actually gave him some chloroform (bad treatment probably), in order to establish an intravenous drip and keep it there for a time. His violence required restraint by nurses, students, porters and myself for thirty-six hours to enable necessary insulin, fluids and occasional tests to be carried out. He was given, rather arbitrarily, 25 units four-hourly, became calm and ketone-free in 36 hours and recovered normal cerebration in another 12 hours, i.e., after 48 hours of treatment.

Other cases, varying in age from 9 to 62, have followed the same course but usually for a shorter time. Sodium amytal (5 grains intravenously) or paraldehyde intramuscularly, have helped considerably but sometimes failed to produce real sedation. On the hypothesis that large doses of insulin suddenly changed fat to carbohydrate metabolism and so produced a deficiency in vitamin B, large doses of B_1 and the total B complex have been given without obvious effect. The clinical condition has suggested concomitant meningitis or some intracranial lesion, but no physical evidence of this has been found and lumbar puncture in three cases has shown a normal spinal fluid, apart from an excess of glucose and ketones. I should think that changes in potassium, although not investigated, could be ruled out. Whether dehydration, present in all, or hyperglycemia or ketosis is the trigger factor is speculative. But experience of myself and my assistants, has too often encountered this maniacal phase of diabetic coma, which is not recognized in the literature.

ACUTE ABDOMINAL PAIN IN PRECOMA

The "acute diabetic abdomen" is the name I gave to this condition many years ago. Although it is familiar to those who handle large numbers of diabetics, it is a rare condition as shown by the fact that an abdominal surgeon of twenty years' experience met it for the first time in one of my diabetics this year. He telephoned me at 3 a.m., saying that he had just seen a diabetic boy of mine with an acute abdominal condition (possibly appendicular in origin) and peritonitis, for which he must operate at once, asking that I deal with the diabetes. The urine was loaded with sugar but the ketosis was not known. When I arrived I found the urinary ketosis extreme but only slight dehydration. The boy was nearly fully conscious but writhing in pain. The abdomen was rigid and tender all over and the pain was increased by palpation. The diaphragm was fixed but an attempt at air hunger was made by the accessory chest muscles of respiration. The history showed increasing vomiting for some twenty hours and intense pain for only two hours. The usual

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insulin had not been omitted but the blood sugar was 825 mg. per cent. The usual treatment with repeated doses of insulin and intravenous saline, and later glucose and saline solutions, removed the intense pain in ten hours, the ketosis completely in twenty hours but the coma deepened and remained profound for thirty-six hours—a common happening. But within a week he was well and nearly back to his usual dose of insulin with no evidence of any abdominal lesion.

In my experience the abdominal rigidity is usually generalized but the location of the chief pain and tenderness is variable, often suggesting appendicitis or a perforated peptic ulcer. But in one patient the pain was in the right upper quadrant and referred to the right shoulder, suggesting gall bladder or diaphragmatic trouble.

The diagnosis is difficult because, although the degree of ketosis could explain the symptoms, a concomitant inflammatory lesion might also be present. I have twice been wrong and missed a fulminating appendicitis for many hours. Unfortunately a blood count is no help as a polynuclear leucocytosis as high as 40,000 may be produced by uncomplicated diabetic acidosis.

It is helpful to remember that the abdominal pain is usually preceded by some hours of vomiting in the "acute diabetic abdomen" whereas the reverse sequence is commoner with an abdominal lesion.

Treatment consists first of the usual procedures to overcome ketosis and dehydration. By the use of antibiotics the delay in attacking surgically any intra-abdominal lesion which may become obvious later is much safer than it used to be. So at first the surgeon's hand should always be stayed. The exact mechanism that produces this pain remains obscure.

INTENSE LUMBAR PAIN

Although minor lumbar pains are not uncommon in severe diabetic acidosis I have only twice seen intense pain which dominated the clinical picture because of the localized agony produced. Both cases were women about thirty years old. In one instance the family practitioner was called in for this terrible but puzzling pain and finding heavy glycosuria admitted her under my care. She had not been vomiting, showed no serious dehydration, but when I found a severe diabetes with extreme ketosis I started emergency treatment at once, i.e., insulin, and fluids by mouth.

The agonizing pain was confined to the area of a fist in the lower lumbar area, did not radiate, was not increased by pressure and was hardly affected by morphine. Although some inflammatory lesion of the lower spine or meninges was suspected, all tests of the central nervous system were negative and a later examination of the cerebrospinal fluid was normal apart from an excess of sugar and ketones. After twelve hours, when ketosis was completely absent and hyperglycemia approaching normal, the lumbar pain had gone completely. The other case ran the same course, but no lumbar puncture was done.

DEEPENING UNCONSCIOUSNESS DURING TREATMENT

This happening caused me great anxiety when I first observed it thirty years ago and still perturbs the resident physicians in training and others meeting it for the first time. A patient somewhere between pre- and complete coma is admitted with remnants of consciousness, may half answer a question, make some movement in response to stimuli, and is certainly not in complete unresponsive coma. As the necessary treatment, insulin, fluids and minerals, proceeds and as the chemical disturbances of coma are lessened and ultimately removed, unconsciousness sometimes deepens and becomes profound apart from any hypoglycemia as proved by blood sugar estimations. This phase may last from 12 to 24 hours and again I have no adequate explanation. It probably has no relation to the lowered potassium often found in the latter phases of rehydration. Most of these cases occurred before any attention had been drawn to hypokalemia and they recovered normal cerebration slowly without its administration. Nor has the full administration of the vitamin B complex in a few cases seemed to hasten mental recovery.

EPILEPTIFORM CONVULSIONS

I have met this only once as a complication of diabetic coma and this is fully described and discussed in the following article. In view of the last electro-encephalogram it seems that the coma touched off an underlying epileptic diathesis.

SUMMARY

Five rare clinical manifestations occurring in diabetic coma and precoma are described.

SUMMARIO IN INTERLINGUA

Rar Manifestationes Clinic in Coma e Precoma Diabetic

Es describite cinque rar manifestationes clinic, occurrente in coma e precoma diabetic.

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Convulsions During Diabetic Ketosis

A Case Report

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The diagnosis of diabetic coma is seldom difficult, but may be so when there are bizarre signs or symptoms or in the presence of intercurrent disease. A clear-cut history of diabetes accompanied by dehydration, acetone in the breath and air hunger, enables the diagnosis to be made with reasonable certainty before the results of laboratory studies are available. The importance of early diagnosis does not need to be emphasized. But a patient who is mentally confused or violent, in whom there may be an additional cause for coma, can present problems in both diagnosis and treatment. Troubles of this nature arose when a newly diagnosed diabetic had a series of epileptic fits while in coma. This case is reported herewith.

CASE HISTORY

One month before admission this forty-six-year-old woman noticed loss of weight and constipation, for which she underwent gastrointestinal investigations at another hospital. For two days before admission to King's College Hospital she had complained of thirst and polyuria. Ten hours before arrival she became comatose after a brief period of irrational behavior, and when examined appeared to be in severe diabetic ketosis. As she was being transferred from the ambulance a nurse suggested that there might have been a short generalized convulsion, the significance of which was not immediately realized. No personal history of other significant disease was obtained, but a maternal grandfather was known to be diabetic.

Physical examination. She was severely dehydrated, smelled of acetone, had air hunger, was deeply comatose and in a state of vascular collapse with blood pressure 80/60 mm. Hg and mouth temperature of 95°F (35°C). Both plantar reflexes were extensor and an unusual finding in diabetic coma was considerable inequality of the pupils, which did not react to light.

Initial laboratory investigations. Urine: Sugar ++++; Rothera +++; Gerhardt +++; Albumen +. Blood electrolytes: Serum sodium 153; potassium 4.3; plasma chlorides 123; alkali reserve 6 mEq/L; blood urea 54 mg./100 ml. Blood sugar: 860 mg./100 ml., (Folin-Wu).

Treatment and progress. Soluble insulin was given immediately, 100 units subcutaneously and 40 intravenously, and intravenous 0.9 per cent saline was commenced. Before any appreciable quantity of fluid had been given she had a generalized epileptic fit with tonic and clonic phases during which she became deeply cyanosed. The blood sugar at this time was 890 mg. but she was given 20 gm. of glucose intravenously, followed by 2.0 gm. of calcium gluconate, intramuscular vitamin B complex, and 180 mg. of sodium phenobarbitone, the saline infusion being continued. Five hours later after 80 additional units of soluble insulin her blood sugar had fallen to 540 mg. and her blood pressure was 130/80 mm. Hg. Unfortunately in the next twelve hours she had eight more convulsions in spite of sedation. In none of these was the blood sugar low nor were there signs of tetany or persistent alteration in muscle tone. Although her stomach had been aspirated she inhaled vomitus and required simultaneous gastric and endotracheal suction for prolonged periods. Later that night she was more deeply comatose than expected in view of the biochemical and circulatory improvement, but there were still no signs to suggest localized intracranial disease other than inequality of the pupils. She regained consciousness after thirty-six hours with no serious disabilities. For the following two years she has remained well and the diabetes has been stable with about 40 units of insulin zinc suspension (Lente) daily.

Other investigations. Lumbar puncture (second day): Pressure 120 mm. water; Queckenstedt's test positive; white blood cells 1 per cmm; protein, 30 mg./100 ml.; Wassermann negative; Lange, zero curve. Skull X ray: normal. Chest X ray (on admission): normal. Hb.: 130 gm./100 ml. Serum calcium: 9.8 mg./100 ml. Electro-encephalograms (EEG): 1. (third day) An abnormal record with irregular low potential theta activity at 3 to 7 cycles per second (c.p.s.) and short bursts of 2 to 3 c.p.s. activity in the temporal region. No specific diagnosis was suggested. 2. (twenty-eighth day) Less abnormal with 9 to 10 c.p.s. Alpha activity of up to 60 microvolts dominant posteriorly, plus excessive theta activity of a lesser degree than previously. 3. (two years) Still a little abnormal but there has been further improvement since the first tracing. There is an excess of theta activity at 3 to 6 c.p.s. but there are no localizing signs and the appearances are in favor of a constitutional abnormality, compatible with latent epilepsy.

DISCUSSION

The course of diabetic ketosis is usually gradual and restlessness or violence is fortunately rare. We have not previously encountered a patient in whom epileptic fits developed during hyperglycemia without there being an additional cause. Were these convulsions to be attributed to the metabolic upset or to some other occult disease? The severity of the ketosis, depletion of alkali reserve, the blood sugar of 890 mg. and the characteristic history strongly suggested diabetes mellitus rather

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than a disturbance of carbohydrate metabolism secondary to an intracranial lesion. Since the first fit occurred before treatment had begun such causes as air embolism or unusual drug sensitivity could be excluded. The possibility of intracranial disease was considered carefully, but the absence of papilledema and localizing neurological signs and the subsequently normal cerebrospinal fluid ruled out subarachnoid or cerebral hemorrhage, meningitis, and brain abscess or tumor. It was also unlikely that cerebral thrombosis secondary to dehydration was responsible since as time went on there were still no signs of residual damage.

Another possible factor was pyridoxine deficiency, in spite of the absence of obvious evidence of vitamin B deficiency. Although Gyorgy[1] considers that such a deficiency in adults does not induce fits as in children, Coursin[2] has shown that the abnormal electro-encephalogram found in infants with epilepsy due to lack of pyridoxine will return to normal within five minutes of injecting the vitamin. The persistently abnormal EEG in the absence of fits rules out such a cause in this patient.

Other etiological factors considered included hypoglycemia, magnesium deficiency, intracellular electrolyte imbalance, anoxemia and of course idiopathic epilepsy. Hypocalcemia should have responded to intravenous calcium gluconate, and in the lack of a serum calcium estimation at that time the absence of tetany provides good evidence against such a disturbance. Without appropriate studies we can not say whether or not magnesium deficiency might have been present. Urinary loss of magnesium is known to be high during the polyuria of untreated diabetes, and in animals and man depletion leads to increased muscular excitability and to convulsions.[3] The administration to our patient of cellular repair fluid containing 240 mg. of magnesium chloride per liter did not appear to do any good. Intracellular overhydration or sudden changes in relative osmolarity may certainly provoke convulsions in the idiopathic epileptic, but this woman's attacks began when she was dehydrated and continued after fluid and electrolyte balance had been returned toward normal. Gans[4] thought that some such fluid-electrolyte imbalance affecting the cerebral cortex might have been responsible for the fits which he observed in a twenty-one-day-old ketosed diabetic infant. Lastly hypoglycemia, a potent epileptic trigger, can be excluded since the blood sugar during the first fit was 890 mg. and 260 during the last, and at no time was there a response to intravenous glucose.

We were therefore at a loss to explain these convulsions and could do no better than treat the diabetes on conventional lines, taking care to avoid hypoglycemia, and giving sedatives to reduce cortical excitability. The discovery of the abnormal EEG on the third day was of interest but it was still difficult to decide whether the record was a sequela of diffuse brain damage or an indication of latent epilepsy. The studies of Izzo[5] were relevant since he had shown that no characteristic EEG pattern was to be expected in diabetics after episodes of hyperglycemia with blood sugars of over 400 mg. per 100 ml. At the time of the second tracing she was in good health and adequate diabetic control, but the findings were still not normal. After three months there was a further improvement in the EEG, but two years later the excess of theta activity persisted and was thought to be compatible with an epileptic constitution.

Why should this woman have a disastrous series of fits while severely ketosed, having been free of such attacks all her life? Acidosis is a factor in reducing cortical excitability and in former days ketogenic diets were used to control idiopathic epilepsy. The observations of Kety et al.[6] that cerebral anoxemia could occur during diabetic coma in spite of a normal or increased cerebral blood flow are pertinent. Lawrence et al.[7] pointed out the histological similarity of the cerebral changes seen in cases of fatal hypoglycemia and in anoxemia, and suggested the term *oxyachrestia* to indicate inability to utilize oxygen secondary to the lack of glucose. Yet if cerebral oxygen lack was a factor in this case it is difficult to understand why fits should be so rare during diabetic coma, particularly in the epileptic. The exact cause of this woman's trouble remains uncertain. The persistently abnormal EEG suggests that she has a constitutional predisposition to epilepsy and that the metabolic disturbance of diabetic coma was the trigger mechanism. In exceptional instances it may be permissible to attribute convulsions to diabetic ketosis in the absence of other signs of disease, but such an occurrence is rare.

SUMMARY

A forty-six-year-old woman with a short history of diabetic symptoms developed severe ketosis and became comatose. Before and during treatment she had a series of major epileptic fits over a period of twelve hours, no cause for which could be determined. In the absence of other disease these appear to have been due to latent idiopathic epilepsy with the metabolic disturbance of diabetic ketosis in some way acting as the trigger mechanism.

SUMMARIO IN INTERLINGUA

Convulsiones Durante Cetosis Diabetic: Reporto de Un Caso

Un femina de quaranta-sex annos de etate con un breve historia de symptomas diabetic disveloppava sever cetosis e deveniva comatose. Ante e durante le tractamento, illa habeva un serie de major accessos epileptic, occurrente in le curso de un periodo de dece-duo horas sed non associabile con ulle causa apparente. In le absentia de altere morbo, il pare que le accessos esseva debite a latente epilepsia idiopathic e que le disturbation metabolic de cetosis diabetic ageva in un maniera o un altere como mechanismo precipitatori.

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EDITORIALS

DIABETIC NEUROPATHY

Although the neurologic manifestations have been recognized in diabetes since 1864, they have not received the detailed analysis usually given to other neurologic conditions. Because of their frequency they are entitled to more attention. Among the twenty million estimated diabetics throughout the world undoubtedly there are probably hundreds of thousands of cases of "diabetic neuropathy." The latter term is generally applied rather loosely, referring to involvement of peripheral nerves only (in the previous sense of "neuritis") in some instances and to more widespread involvement (both motor and sensory) emanating from spinal cord lesions in others. Garland urges that the designation neuropathy be restricted to disorders of the peripheral nerves leaving "myelopathy" for cases in which the cord alone is involved.

In 1953, Garland and Taverner reported three diabetic patients suffering from a purely motor disorder which appeared to them to be a syndrome probably of cord origin. The patients were over fifty years of age and gave a recent history of diabetes of mild degree. The neurologic picture was limited to the legs and included diffuse pain, weakness, atrophy and areflexia, and usually it was asymmetrical. Other features which appeared less constantly were extensor plantar responses, an elevated protein content of the cerebrospinal fluid, and electromyographic changes in the affected muscles. In none was there any sensory loss. The condition was found only in patients who, though usually being treated, had not been strictly regulated. At the same time manifestations were largely or totally reversible.

Subsequently, Garland reported twelve cases suffering from this neurologic entity (*British Medical Journal*, Nov. 26, 1955). The findings were not always limited to the lower extremities, the upper extremities being affected occasionally. Because the manifestations were not always uniform the author selected the term "diabetic amyotrophy" in preference to myelopathy to describe this condition. Although most of the author's cases had been overlooked, probably because it does not coincide with other more readily recognizable neuropathies, the syndrome is by no means rare. Other diagnoses which were tentatively considered by referring physicians in these cases were sciatica, lumbar arthritis or motor neurone disease. The condition is always reversible with the achievement of total diabetic control. Recovery is somewhat hastened by use of exercise, calipers and crutches.

Garland stresses the use of electromyography as a diagnostic aid. Affected muscles showed electromyographic changes in all cases which are subject to wide variations suggesting a cord lesion in some cases but not

so in others. Regardless of the nature of the electromyographic changes the distribution of the weakness, atrophy and areflexia followed a similar pattern. The authors point out that in diabetic neuropathy the sensory fibers of the peripheral nerve are generally affected, but he also envisions the possibility that diabetes can produce purely motor changes in the peripheral nerves.

In this regard, I should like to call attention to a strikingly similar syndrome which I described in 1954 entitled "Femoral Neuropathy in Relation to Diabetes Mellitus: Report of 17 Cases" (DIABETES 3:266-73). These cases were likewise characterized by pain and tenderness along the cutaneous branches of the femoral nerve, weakness and atrophy of the quadriceps muscles and patellar areflexia. Although the cerebrospinal fluid was not examined routinely in these patients a significant elevation of the protein content was found in three cases, a finding which was considered significant. A positive femoral nerve stretch test proved to be a valuable diagnostic aid in many of these patients. Although so-called diabetic tabes had been suggested as a diagnosis in some of these cases and herniated intervertebral disc in others, in our opinion this syndrome represents a peripheral neuropathy or neuronopathy. Aside from the clinical involvement of the femoral nerve, other features which seemed to favor a peripheral neuropathy rather than a spinal cord lesion are the reversibility to normal of the symptoms and signs and the selectivity of various fibers (e.g., motor fibers) within the nerve. Aside from an anterior horn involvement (which is unlikely to be completely reversible) it is difficult to visualize within the spinal cord a lesion of such selectivity as to involve modalities such as the patellar reflex and pain without affecting at the same time other sensory modalities. Furthermore, it is difficult to visualize in those patients who complain of pain and paresthesia in the lower extremities just how these symptoms could be explained by an anterior horn lesion or a purely cord lesion for that matter. One must envision, over and above any cord involvement, that the sensory symptoms probably take their origin in peripheral nerves or sensory roots.

The cases which serve as the basis of Garland's very excellent, thought-provoking report appear to show a striking similarity to those which we encountered with femoral neuropathy. Certainly, the most striking features of his cases—weakness and atrophy of thigh muscles, areflexia and the close association with unregulated diabetes—were present also in ours. The presence of pain and the elevation of the cerebrospinal fluid protein in some cases also occurred in both series. Finally, the reversibility of the manifestations as a result of meticulous diabetic control is another point of total agreement in the two groups. Although Garland has called attention to an interesting, possibly a new syndrome, the question as to whether it is truly a myelopathy in some instances, as this author suggests, or an extensive neuropathy (neuronopathy), extending up into the nerve roots in some cases, still remains to be settled.

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GALACTOSEMIA

Galactosemia is a congenital disorder characterized by an inability to metabolize galactose normally. The earliest cases were reported by von Reuss[1] in 1909 and Goppert[2] in 1917. Mason and Turner[3] described the first case in the American literature in 1935. Since that time several patients have been reported and there is reason to believe that many more well documented cases have not been reported.

Infants with galactosemia usually are not ill during the first several days of life. Then signs of growth failure appear even though the appetite remains good. Enlargement of the liver, often accompanied by jaundice, gradually appears. The jaundice may seem to be prolonged "physiologic" jaundice of the newborn and frequently is transient, subsiding after a variable period of time. Splenomegaly, ascites, low plasma protein, and abnormal liver function tests may be found. Lamellar cataracts develop with a high degree of frequency if the disorder is not recognized and treated early. Mental retardation may be present, sometimes without relation to severity of disease or to onset of treatment. The galactose tolerance curve is prolonged and elevated in all cases. Normocytic anemia and osteoporosis have been reported in some cases. Amino-aciduria, apparently due to diminished tubular reabsorption, has been described.[4]

Reducing substance in the urine is invariably present (although not necessarily in every specimen) and is an important clue in early recognition of this disease. Negative yeast fermentation and the formation of specific osazone crystals with phenylhydrazine will identify the reducing substance as galactose. Recently devised enzyme impregnated test papers,* specific for the detection of glucose, may be used for simple screening to eliminate this sugar as a source of the melituria.

Early diagnosis and treatment are of prime importance to the prognosis for the patient. Complete removal of

* Clinistix, Ames Company, Inc., Elkhart, Indiana. Tes-Tape, Eli Lilly and Company, Indianapolis, Indiana.

galactose from the diet permits rapid regression of signs and symptoms. Cataracts sometimes persist and require surgical treatment. Although galactose intolerance persists, it becomes less significant as the child grows older, and moderate amounts of this sugar may be tolerated.

In several instances galactosemia has been found in more than one sibling in a family.[5, 6, 7, 8, 9, 10] Holzel and Komrower[5] studied the genetic aspects by administering galactose tolerance tests to all the parents as well as to other relatives of five galactosemic infants from four families. The results of these tests were that at least one parent as well as three of six siblings reacted abnormally. However, all were free of clinical manifestations of the disease. That the disease is genetically determined is strongly suggested, but sufficient evidence is lacking at this time to be sure of the exact mode of transmission. When some of the survivors of infantile galactosemia reach the child-bearing age, much important information about the hereditary aspects may be gained.

Liver biopsy and portmortem examinations have revealed fatty infiltration of the liver[7] and lesions characteristic of portal cirrhosis.[6, 8, 9] It is thought that the deleterious effects of this disease result from some toxic action of galactose. High galactose diets produce cataracts in rats,[11] and convulsions with death in chicks.[12] The hypoglycemia frequently found with hypergalactosemia also has been postulated as possibly injurious.

Galactose-1-phosphate accumulates in the erythrocytes of galactosemic infants after lactose or galactose feedings.[13] Further, in vitro studies reveal the same process by the demonstration of galactose-1-phosphate accumulation in galactosemic infants' red cells incubated with galactose.[13, 14] These investigations indicate the presence of galactokinase in patients with this metabolic defect.

The conversion of galactose-1-phosphate to glucose-1-phosphate is thought to involve the following steps in which a nucleotide, uridinediphospho-glucose, is required.[15]

1. Galactose-1-phosphate + Uridinediphospho-glucose

$$\xrightarrow[\text{PGal transferase}]{} \quad \text{Glucose-1-phosphate} + \text{Uridinediphospho-galactose}$$

2. Uridinediphospho-galactose

$$\xrightarrow[\text{Galacto-Waldenase}]{} \quad \text{Uridinediphospho-glucose}$$

Kalckar, Anderson and Isselbacher[10, 14] recently have studied PGal transferase activity in erythrocytes. By incubation of galactose-1-phosphate and uridinediphospho-glucose with hemolysates, and by subsequent measurement using enzymatic technics, the conversion of uridinediphospho-glucose to uridinediphospho-galactose quantitates PGal transferase activity. By this means PGal transferase activity was found to be present in the erythrocytes of normal children and to be absent in erythrocytes of galactosemic patients. The enzyme was present in all healthy relatives of the patients. Therefore, even though other evidence is consistent with some hereditary pattern of origin, no "trait" could be detected by the method described.

Although definitive studies have not been carried out, it seems probable that the lack of PGal transferase in the red blood cells of galactosemic individuals reflects a similar state in the liver. From the evidence available galactosemia appears to be a genetically determined disease in which a specific enzyme is lacking.

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Frederick William Pavy

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Frederick William Pavy was born on May 29, 1829, at Wroughton, Wiltshire, England. He received the M.B. degree of London University, with honors in physiology and medicine in 1852, and the M.D. degree in 1853. After serving as house surgeon and house physician at Guy's Hospital, he continued his studies in Paris in the laboratory of Claude Bernard already famous for his researches in physiology. Claude Bernard awakened Pavy's interest in experimental physiology, especially in carbohydrate metabolism, which persisted to the end of his life. His first communication to the Royal Society in 1855 was entitled: "An Experimental Inquiry into the Nature of the Metamorphosis of Saccharine Matter as a Normal Process of the Animal Economy." His later papers were concerned with lesions of the central nervous system producing diabetes. Another study from the early research period was entitled: "Experimental Inquiry into the Alledged Sugar-Forming Function of the Liver." As his systematic experimental research went on, Pavy came to disagree with Bernard's views of the glycogenic theory of diabetes.

His classical book, *Researches on the Nature and Treatment of Diabetes,* written almost one hundred years ago (1862, republished 1869), presents a summary of his experimental work and of his theories of diabetes. He proved that during life the blood of the right heart does not contain more sugar than that in other parts of the circulation. He thus eliminated the basis of the theory, prevalent at that time, that the lungs are responsible for the combustion of sugar. He maintained that the metabolic error of diabetes is caused by "mal-assimilation of sugar." According to this theory, failure to incorporate sugar into the large molecules of protein results in diabetes, in accumulation of free glucose in the circulation and by necessity in its excretion in the urine. In extensive and meticulous studies Pavy was able to demonstrate small quantities of sugar in the urine of normal persons, in his opinion a most significant finding. He described extensively the laborious studies devoted to the carbohydrate fraction in serum proteins.

To the clinician his book on diabetes is of particular interest because of a very careful analysis of the symptomatology of human diabetes. Polyuria and polydipsia and their relation to the concentration of glucose in the urine and to the specific gravity are extensively discussed. Such details as white spots left on articles of clothing "where drops of urine had fallen," the type of thirst that cannot be quenched, however much fluid is taken, "a peculiar sensation, not exactly hunger, referred to the stomach, which the diabetic is generally well acquainted with," the changes of mouth and tongue, the sweet taste, changes of the skin and "a peculiar odour eliminated from the body of the diabetic," are discussed. In his experience the "odour of the diabetic resembles the smell of ripe apples more than anything else." It may be safely assumed that many of Pavy's patients exhaled acetone in their breath. Questions of diet interested him greatly. He stressed the necessity of eliminating carbohydrates from the diet because of his concept that in diabetes these foods are not assimilated properly. He used gluten and almond bread as substitutes and introduced codeine as a substitute for opium in the treatment of diabetes. The book includes many recipes for carbohydrate-free dishes and a careful discussion of various menus. His book on diabetes remained for many years the standard book in the field.

In 1874 Pavy published his second important monograph entitled: *Treatise on Food and Dietetics* (second edition 1875). Without presenting too much original research the book gives a good account of the knowledge of nutrition approximately ninety years ago and has a sound physiological basis. There is an interesting discussion of foods eaten by the inhabitants of various regions including the arctic, by Indian tribes, the natives of Australia, China, Japan, Egypt, and Abyssinia. A chapter on practical dietetics includes an elaborate discussion on proper quality and quantity of food, on culinary preparation of food, on diets for thinness and stoutness, for gout and diabetes. An appendix presents the dietaries used in the various hospitals of England; it affords an excellent illustration of the customs and habits of that time. Pavy's treatise on food and dietetics became a second standard book for many years and makes interesting reading today.

Pavy's interest was not confined to the subject of carbohydrate metabolism and diabetes. His name is associated with the recognition of postural albuminuria and with the immunity of the gastric mucosa to autodigestion. As a pupil of Claude Bernard he realized that understanding of the normal processes in the body

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is a necessary prerequisite for the study of disease. He was methodical, punctual, precise and "never in a hurry." He performed his duties in a large hospital and medical school, Guy's Hospital in London, and had an extensive private practice especially among the sufferers from the disease to the study of which he devoted most of his life. Even in his old age he spent much time doing research in diabetes. In 1905 he presented a paper, "The Pathogeny of Diabetes," before the International Congress of Internal Medicine. His final paper was published in 1911 and its title was: "Some Recently Elicited Facts Relating to Carbohydrate Metabolism and Glycosuria." He died in London on Sept. 19, 1911, in his eighty-third year.

Pavy was one of the prominent physicians of the second half of the past century. He was a worthy successor of Prout and Bence Jones and a contemporary of Garrod and Thudichum. His leading role in medicine may be characterized as that of a clinician-chemist who built the foundations and advanced the study of metabolism mainly by applying new experimental technics and advances in physiology to research in clinical medicine. He was the founder of the modern study of diabetes.

Robert Russell Bensley, 1867-1956

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Not "who is right, but what is right" characterized the life of Dr. R. R. Bensley. The effect of this philosophy upon the lives and attitudes of his students and their students constitutes a truly effective memorial. Dr. Bensley had the wisdom and patience to refrain from engaging in polemics, allowing time to prove his theses; he had the longevity to see many of his important discoveries first ignored, later accepted, and finally acclaimed.

Dr. Bensley was born of an English-Canadian father and Irish mother on a farm near Hamilton, Ontario, on Nov. 13, 1867. His vigorous boyhood included farming in summer and logging in winter. He attended country schools and the Collegiate Institute in Hamilton. At the age of sixteen he left for Toronto to enter the University College where he participated in college life with zest. He registered for all the courses in chemistry, languages, arts and sciences that were given. Obviously some of the classes were rarely or never attended, but he passed the courses by examination.

In his third year of college, while pursuing a favorite hobby, hunting, he suffered a severe gunshot wound of the leg. He applied a tourniquet himself, thus preventing bleeding to death from a severed artery. A noted surgeon of the day was summoned and he amputated the shattered leg below the knee. The operation was performed on the dining room table of the farm house. Following the surgery gangrene set in, and another amputation high in the thigh had to be performed. Following this there developed thrombophlebitis, septicemia and bacterial endocarditis. The surgeon left a pound of opium with the family with directions to keep the patient comfortable and left the young man to die in peace. However, the patient regained consciousness and with it a determination to live. In about two weeks he recognized his dependence on the narcotic and suspected that it might be the cause of many of his symptoms; therefore, he refused to take any more. By sheer will power he survived about four days of torture after which his recovery was progressive and complete.

His convalescence took about a year. During this time he did a prodigious amount of reading. His father bought him a microscope and a few inexpensive accessories. He learned how to make dyes out of bark and fruit and to stain preparations with them. His preparations were mounted with balsam collected from the blisters of a Canada balsam tree growing in the front yard. This year's activity set the pattern and direction for much of his life's work.

In the fall of 1888 he returned to University College and was graduated with honors in 1889. He won the Governor-General's medal in both arts and sciences and a prize in both chemistry and languages. His interest in and facility for language was maintained throughout his life. His aptitude for chemistry enabled him to become an expert in the chemistry of dyes and it

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provided a chemical point of view which became so prominent in his later work.

He entered medical school at Toronto in 1889 and while he was a medical student he found time to begin his original investigations in the Department of Biology and to teach histology to the medical students. The year 1892 was an eventful one. In that year Dr. Bensley received his medical degree, married the pretty Carriella May, started the practice of medicine and continued to teach at the University of Toronto. He served on the faculty of the University of Toronto in the Department of Biology for ten years as an assistant demonstrator and demonstrator.

In 1901 the Canadian government asked him to design, build, and equip a Marine Biological Laboratory on the Georgian Bay. That summer he sold his island in the Muskoka Lakes and bought one at Gohome Bay. There he built a summer cottage for his family and supervised the building and equipping of the Marine Laboratory. A summer cottage was always of extreme importance, for Dr. Bensley had a rare ability for combining work and play and he spent his summers collecting zoological and botanical specimens, fishing, hunting and exploring, as well as working on manuscripts.

In the autumn of 1901 he moved to the University of Chicago as an assistant professor in the Department of Anatomy. He became acting chairman of the department in 1905 and director of the laboratories of anatomy in 1907. He obtained his U.S.A. citizenship in 1916. In 1918 he was president of the American Association of Anatomists, and in 1919 he received an honorary Doctor of Science degree from the University of Toronto. He retired from the University of Chicago in 1933 after thirty-two years of service. During the more than twenty years that followed his retirement, Dr. Bensley continued an even more active and productive research career. Because of recurrent attacks of thrombophlebitis Dr. Bensley's good leg had to be coddled during many of the remaining years of his life. However, this seeming handicap never interfered in any way with long and regular hours in the laboratory, or the continued pursuance of his hobbies of hunting and fishing.

Dr. Bensley published approximately fifty papers in his lifetime and his research covered an extremely wide range of interest. There never were publications just for the sake of writing papers; only the most important of his investigations were published. His contributions to fundamental knowledge, however, were enormous and few scientists have been able to do so much in a single lifetime. Of all his contributions it is probable that his studies on the islets of Langerhans and the separation of mitochondria have had the greatest impact and stimulated the largest number of investigators.

The research which was carried out in 1892 was on the microchemical reaction for masked iron, and although this reaction does not bear his name it was one of the earliest attempted studies in histochemistry. In 1896 he published his first paper on the gastric glands and received a warm letter of congratulation from Sir William Osler; this was a great stimulus for the young scientist. There followed in 1896-1903 a series of papers on the histology of the gastrointestinal tract which included the identification of the gastric mucosa neck cells and a detailed study of the cardiac, gastric, and duodenal glands of Brunner. His studies on the Golgi apparatus in 1910 and his later paper in 1929 on "Osmic Acid as a Microchemical Reagent, with Special Reference to the Reticular Apparatus of Golgi" placed the existence of this cell organelle on a solid footing. His classical paper on "Studies of the Pancreas of the Guinea Pig" was published in 1911 and amplified in his Harvey Lecture publication of 1915. From 1912 to 1913 he reported on the mechanism of hydrochloric acid secretion by the stomach; these studies were extended in 1936. From 1914 to 1916 Dr. Bensley was the first to demonstrate the presence of secretion granules in the thyroid cell and he showed that the cytological position of these secretion granules varied with the physiological state of the gland. These fundamental studies of thyroid cytology have ultimately provided the basis for a more adequate understanding of the action of thyroid drugs and the treatment of thyroid disease. He published a paper on "The Nature of Rouget Cells of Capillaries" in 1928 and several papers on the histology of the kidney in 1928-1931. In 1931 he reported on the histology and pathology of an islet cell adenoma removed from a patient with clinical hypoglycemia.

The freezing-drying method, earlier described by Altman but long since forgotten, was reintroduced in Bensley's laboratory. In 1933 and 1934 there followed a series of cytological and chemical studies on the organization of the cell using the freezing-drying method. The isolation of mitochondria from the liver cell was reported in 1934 one year after his official retirement. This came as the culmination of Dr. Bensley's keen interest in this cell organelle which had begun in 1910-1911 with a study of the supravital staining of mitochondria with Janus Green. In the two decades that followed his retirement Dr. Bensley continued working in the field of cytochemistry and he published several papers on the "Fat Distribution in Mitochondria"; on

the "Gel and Fiber Forming Protein Constituents of Protoplasm," and on the "Chemical Structure of Cytoplasm." He continued working in the laboratory with his own hands until a few months before his death at the age of eighty-eight.

Dr. Bensley gathered about him a number of graduate and medical students. Many of the above studies were carried out with their collaboration. In addition, a great many of the papers which appeared from the Department of Anatomy at the University of Chicago were Bensley-inspired even though they did not bear his name. A considerable number of his former students have since become professors of anatomy, and many have become leaders in their respective clinical fields.

To students of diabetes, however, Dr. Bensley is best known for his work on the pancreas, for these studies provided much of the basic knowledge which led to the discovery of insulin. Before Bensley's studies, the literature on the islets of Langerhans of the pancreas was confusing and contradictory. For, although Laguesse had early suggested that the islets of Langerhans had an endocrine function, many prominent investigators who followed Laguesse determinedly maintained that these islets simply represented the exhausted state of the secretory acini of the pancreas and that the size and number of the islets varied with both the secretory activity of the pancreas and with the nutritional state of the animal. The status of the islets of Langerhans, following duct ligation of the pancreas, was in a similar state of confusion. The published reports were so diametrically opposed that a reviewer, in summarizing the effects of duct ligation, simply divided the investigators into three groups and designated them as (1) authors reporting that duct ligation preserved the islet tissue only; (2) authors reporting that neither the islet nor the acinar tissue was preserved; (3) authors reporting that both islet and acinar tissues were preserved.

Dr. Bensley approached the problem of the islets of Langerhans by developing new methods for the study of the pancreas. He developed supravital technics for staining all of the islets in a pancreas and devised methods for staining the duct system by vital dyes. By combining these methods he was able to stain simultaneously the islets and ducts in the same preparation. He also developed several cytological staining methods which permitted the selective staining of the alpha and beta cells in the islets of Langerhans. These methods and technics made it possible to count the number of islets, to study the functional changes in the islets of Langerhans and to determine their relation to the ducts. Dr. Bensley's work cleared up the controversy which had been raging on the significance of the islet tissue and it clarified the cytological changes that take place in the pancreas following duct ligation. Dr. Bensley's work left no doubt that the islets of Langerhans were independent structures which had an endocrine function. He said:

We can now state with assurance that the islets of Langerhans are specialized elements of the pancreas, having secretory powers differing from those of the acinar tissue, developing in embryonic life from the undifferentiated epithelium of the pancreatic anlagen and in postfetal life from the epithelium of the ducts. The islets have a peculiar blood supply characterized by its direct arterial source, by the larger calibre of its capillary vessels, and by the close association of the latter with the epithelial cells. These experimental morphological studies give us no information as to the nature of the internal secreting function which is obviously indicated by their structure. For enlightenment on this topic we must look to further experimental work.

It was in the light of these fundamental studies on the pancreas that Banting was successful in isolating insulin from the duct-ligated pancreas in 1923. It was then that "insulin discovered Bensley" for the reprints of his fundamental work on the pancreas which had collected dust since 1911 were all requested and distributed in a matter of a few months. Dr. Banting fully appreciated the importance and significance of Dr. Bensley's studies. At a Nobel Prize Celebration Dinner in Toronto commemorating the discovery of insulin, Banting is reported to have told Bensley: "You know, Dr. Bensley, it was your Harvey Lecture on the pancreas that gave me the courage to go ahead with my experiments when all others told me I would fail."

Dr. Bensley was fully cognizant of the enormity of the diabetes problem and his prediction made in 1915 has been fully borne out. At that time he wrote:

. . . interest has centered around the phenomena of diabetes, and workers have sought by various experimental methods to show that the work done by the pancreas in connection with the control of carbohydrate metabolism was the function in particular of the islets of Langerhans. That this is a narrow point of view whether we regard it from the standpoint of the derangements of metabolism in diabetes or from the standpoint of the internal secretory activity of the pancreas is obvious, for the fact that the islets are themselves composed of two independent sorts of internal secretory cells would be sufficient to suggest that their internal secretory function is twofold, and many studies indicate that there is more to diabetes than a deficient utilization of carbohydrate material.

This statement, made over forty years ago, is remarkably pertinent today for there is little doubt that the diabetes problem is far more complex than was thought to be the case in the years immediately following the discovery of insulin. The presence of a second cell type in the islets of Langerhans led many investigators to continue their search for another pancreatic hormone and the more recent isolation of glucagon has fully confirmed Bensley's predictions made on the basis of his anatomical studies. It is probable that glucagon originates in the alpha cells of the islets of Langerhans; although its role in diabetes and in human physiology is not completely understood, its function is now being actively investigated.

On June 7, 1952, the American Diabetes Association honored Dr. Bensley with the award of the Banting Medal for the "great service he rendered in the field of diabetes." He was also elected to honorary membership in the Association.

Although Dr. Bensley's official retirement began in 1933, this was just the opportunity he needed to give his undivided effort to the problems which had intrigued him for years and which were to become fertile fields for future investigators in anatomy, biochemistry and cell physiology. Until the work of Bensley, the problem of the localization and spatial relationship of the enzymes within the component parts of the living cell was largely conjecture. The paper entitled "The Preparation and Properties of Mitochondria" published in 1934 employed the differential centrifugation technic for the separation of mitochondria and other morphologically intact component parts of the cell. This study opened new vistas in biochemical and cytochemical research. In 1934 the word mitochondria was virtually unknown to the biochemist; some ten years later the biochemists were just beginning to exploit actively this new medium, whereas today "mitochondria" has become a byword among biochemists and cell physiologists. Studies on the metabolic, synthetic, or catabolic processes of the cell are not considered complete unless they also include data on the mitochondrial, or other subcellular sites of localization of cell function.

In 1942 a symposium entitled "Frontiers in Cytochemistry" was held to honor Dr. Bensley's seventy-fifth birthday. The word cytochemistry was invented for this occasion. The papers presented at this meeting were later published in book form (*Biological Symposia X*) as a tribute to Dr. Bensley and it became eminently clear that the separation of mitochondria in 1934 had provided the stimulus for many workers.

Dr. Bensley fully appreciated the broad significance and implications of this work for, in his review article entitled "Chemical Structure of Cytoplasm" published in 1942, he states:

Obviously the possibility of separating mitochondria and particulates, and of isolating the structural proteins for chemical study opens up a rich field for further research. The localization of enzyme and carrier systems, vitamins, and hormones, and the viruses, functional changes in composition, the tracing of radioactive isotopes into the interior of the cell and the further fractionation of the submicroscopic particles by more refined methods all offer inviting opportunities to the inquiring mind.

In spite of the fact that Dr. Bensley spent almost thirty frustrating years convincing colleagues of the existence and importance of mitochondria, it was he, in 1953, when giving the opening address for the Histochemical Society's Symposium on Mitochondria, who warned that investigators must not lose sight of the fact that mitochondria exist within the cell, that the functions of mitochondria must be considered and integrated with the functions of the other component parts of the cell, and that mitochondria must not be elevated to supreme importance of themselves. Again at the age of eighty-five he was demonstrating the clarity of his vision and the keenness and breadth of his own perspective. This incisiveness of mind he kept until his death.

It was not only that he had this capacity himself, but it was his great willingness to share it generously that meant so much to his students and associates. Dr. Bensley was genuinely interested in all the problems that were brought to him and he seemingly had nothing else to do when his aid was requested. He gave his attention generously in helping others probe their problems.

His family, his students and his friends will long cherish these memories of Dr. Bensley. His keen analytical mind and his great generosity, coupled with the firm conviction "Not who is right, but what is right" have set a high beacon to follow.

Dr. Bensley died on June 11, 1956, at the age of eighty-eight. He is survived by his daughter, Caroline May; his son, R. D. Bensley; his daughter-in-law, Dr. Sylvia Holton Bensley; and their twin sons, Robert and Edward, who gave him the title by which he was so affectionately known by so many—Gramp.

There is to be a memorial service in Chicago on the eighty-ninth anniversary of his birth.

Funds are now being raised for the establishment of an annual Bensley memorial award. Contributions may be sent in care of Dr. M. L. Hoerr, Department of Anatomy, Western Reserve University, Cleveland 6, Ohio.

BOOK REVIEWS

NUTRITION AND CLIMATIC STRESS WITH PARTICULAR REFERENCE TO MAN. *By H. H. Mitchell, Professor of Animal Nutrition, University of Illinois, and Marjorie Edman, Instructor in Animal Nutrition in Charge of Literature Survey, University of Illinois. $6.75, pp. 244, Charles C Thomas, Springfield, Ill., 1951.*

This manuscript first appeared in November 1949 under the title, "Nutrition and Resistance to Climatic Stress with Particular Reference to Man." The funds to support this study were supplied by the Research and Development Branch of the Office of the Quartermaster General, Department of the Army.

The book is divided into three sections—Cold Environment, Hot Environment, and High Altitude. In each section physiology of animal and man with respect to that particular environment is outlined. For the student who is interested in a thorough and critical review of the literature pertaining to the influence of environment on muscular work, on physical capacity for work and the nutritional responses to these stresses will find it in this volume. The literary references are extensive and list all of the major contributions to this area.

STRESS. *By Hans Selye and Gunnar Heuser. $20.00, MD Publications, New York, 1955.*

The Fifth Annual Report on Stress by Hans Selye and Gunnar Heuser follows the general form of the previous editions. It contains an initial section by the senior author reviewing the general physiology and pathology of "stress" as viewed in 1955. This is followed by nine special articles by outside contributors, most of which relate to adrenal and hypophyseal function, a section cataloguing the recent literature as to subject matter, and finally an extensive bibliography.

The initial section by Dr. Selye contains much valuable information. It provides an interesting review of current literature as well as introducing new and provocative ideas. However, it suffers seriously from a lack of critical evaluation. For example, his concept is provocative that "derailments of this adaptive mechanism (i.e., hypophysis-adreno-cortical system) are the principal factors in the production of certain maladies which we consider therefore to be essentially diseases of adaptation." Time and available technics have not yet permitted full investigation of the several theoretically possible abnormalities considered by Dr. Selye, but the preponderance of the evidence which he introduces to support the theory is so tangential and/or uncritical that it detracts rather than adds to the hypothesis. Another important defect is the overly elaborate form of the presentation. The plethora of capital letters, A-R, ABA, A-CC, and F-C, are unnecessarily confusing to the reader, eight pages of glossary being required to define the numerous abbreviations.

In his selection of contributors, Dr. Selye's choice has been excellent, and the nine papers add materially to the value of the book. Conn's brilliant description of primary aldosteronism is fittingly included even though previously published elsewhere. The inclusion of certain authors whose opinions differ from Selye's, i.e., Ingle and Stoerk, is of particular interest as it provides the reader with an unusual opportunity to become acquainted with differing viewpoints and to form his own conclusions. There is a certain amount of overlap in the articles submitted by Nelson and by Scharrer with portions of Selye's own review, but the current intense investigative interest in the neurohypophysis, its anatomy, secretion and relation to ACTH, no doubt justifies this degree of emphasis. The inclusion of Spitz's article on the deterioration of infants exposed to a major psychic trauma emphasizes the extensive physical damage which may result from a certain type of emotional stress, but the parallel drawn between the progressively downhill course of these infants and the triphasic character ascribed to the adaptation syndrome does not appear to be close.

The section contributed by Dr. Heuser with the concluding bibliography provides the reader with an extremely helpful cataloguing of the enormous literature pertaining to the subject.

MODERN NUTRITION IN HEALTH AND DISEASE. *Edited by Michael G. Wohl, M.D., Chief of Human Nutrition, Division of Biological Chemistry, Hahnemann Medical College and Hospital; Chief of Nutrition Clinic, Philadelphia General Hospital; Former Clinical Professor of Medicine (Endocrinology), Philadelphia General Hospital and Temple University School of Medicine; Consultant Physician in Medicine, Albert Einstein Medical Center; Chairman, Commission on Nutrition, Medical Society of the State of Pennsylvania and Chairman, Committee on Nutrition, Philadelphia County Medical Society; and Robert S. Goodhart, M. D., Scientific Director, The Vitamin Foundation, Inc.; Physician-in-Charge, Washington Heights Nutrition Clinic, New York City Department of Health, Lecturer in Nutrition, School of Public Health, Columbia, New York. $18.50, pp. 1062, Lea & Febiger, Philadelphia, October 1955.*

This volume is a compilation written by fifty-five different authors. Its predecessor, Dr. Wohl's book on diet therapy, was organized in a similar fashion.

There are basically three divisions to the text, "Normal Nutrition," "Nutrition in Disease," and a short section on what is called "Nutrition in Periods of Physiologic Stress." In a book of this type the difficulty is in the maintenance of continuity of the extremely high standards set by some of the authors.

There is an excellent chapter by Keys on body weight and body composition. This serves as an introduction to the section on "Normal Nutrition." Various phases of this subject, such as the physiology of the gastrointestinal tract, the physiology of hunger and appetite, and the psychology of appetite are discussed thoroughly.

The section, "Nutrition in Disease," is written from a didactic point of view. It presents material which would be extremely interesting and valuable to the medical student who has had no prior contact with this aspect of medicine.

The section on vitamins is excellent and will prove valuable to those physicians who are interested in learning about the recent developments in this important phase of medicine. This volume has a place in all reference libraries and will prove profitable to the reader.

A MODERN PILGRIM'S PROGRESS FOR DIABETICS. *By Garfield G. Duncan, M.D., Clinical Professor of Medicine, Jefferson Medical College; Director of the Medical Divisions of the Pennsylvania Hospital and the Benjamin Franklin Clinic, Philadelphia, Pennsylvania. $2.50, pp. 222, W. B. Saunders Co., Philadelphia, 1956.*

Dr. Garfield Duncan has written in narrative form a most fascinating story of the problems faced by diabetics. As a narrative, it is kindly, sensitive and sincere. It teaches by example and without indulging in undue sentimentality or excessive criticism it clearly shows the imprint that diabetes makes on the varied fabric of human life.

Because the characters are so intensely human their problems become real and lose the impersonal character of vague or improbable possibilities. One might feel that many people might lose some of the points used from teaching because of the interest in the narrative. However, in the second half of the book is given in ample detail, the routines of urine testing, insulin administrations, diet preparation, etc.

This is one of the best books for diabetics. All should be encouraged to purchase and read it. It will give the new diabetic knowledge, the oldtimer refreshment, and both, the courage to continue to do a good job of caring for their diabetes.

EXPERIMENTAL DIABETES AND ITS RELATION TO THE CLINICAL DISEASE: *A Symposium Organized by the Council for International Organizations of Medical Sciences—Established Under the Joint Auspices of U.N.E.S.C.O. and W.H.O. $7.50, pp. 352, Charles C Thomas, Springfield, Illinois, 1954.*

This volume presents the proceedings of a symposium held at the University of Leiden, Holland, under the sponsorship of the Council for International Organizations of Medical Sciences. The symposium was devoted primarily to the experimental aspects of diabetes but, in addition, included a considerable amount of material of clinical interest. The presiding officer was Professor F. G. Young of the University of Cambridge. The participants comprised an all-star array of investigators in experimental diabetes and related fields. In addition, a few participants with a combination of clinical and investigative interests served to establish a tie between the experimental material, on the one hand, and clinical diabetes, on the other.

The volume includes not only formal presentations but also a great deal of interesting and valuable informal discussion, which brings out a number of observations on diabetes that have not yet reached the literature. Discussed are such subjects as the islets of Langerhans, glucagon, alloxan diabetes, adrenal cortical steroids in relation to carbohydrate metabolism and diabetes, the chemistry of glycogen, growth hormone in relation to diabetes, the action of insulin, hereditary aspects of diabetes and the diabetogenic effects of pregnancy. The presentations and discussions on these subjects constitute excellent reviews of old and new work.

The volume is a worth-while addition to the library of any one who has a serious interest in the development of knowledge of diabetes.

ABSTRACTS

Alonso, Lillian G.; and Maren, Thomas H. (Stamford Labs., Res. Div., American Cyanamid Co., Stamford, Conn.): EFFECT OF FOOD RESTRICTION ON BODY COMPOSITION OF HEREDITARY OBESE MICE. Am. J. Physiol. *183*:284-90, November 1955.

Long-term restriction of food in the genetically obese mouse decreases weight gain in growing mice and decreases absolute weight in the adult. This weight deficit is partitioned between fat, protein, and water.

Although the restricted obese mice had less fat than their unrestricted obese siblings, they still maintained body fat concentrations 2 to 4 times as great as their lean siblings who received 1.3 to 2.7 times as much food.

The unrestricted obese mouse has normal total body protein (gm./animal). Restricted obese mice lose protein in proportion to their diminished intake. Absolute depletion of protein (gm./animal) was 25 per cent and 42 per cent for two schedules in which intake was decreased 46 per cent and 74 per cent respectively.

The obese mouse has a lower percentage of body water than its lean sibling, but higher absolute water content. Fasting induces absolute loss of water along with the losses of fat and protein.

These studies suggest that hereditary obese mice have a quantitatively different metabolism from their lean siblings, in that they tend to have a greater storage of fat per unit of ingested food.

Ashmore, James; Hastings, A. Baird; Nesbett, Frances B.; and Renold, Albert E. (Dept. of Biol. Chem., Harvard Med. Sch., Boston, Mass.): STUDIES ON CARBOHYDRATE METABOLISM IN RAT LIVER SLICES. VI. HORMONAL FACTORS INFLUENCING GLUCOSE-6-PHOSPHATASE. J. Biol. Chem. *218*:77-88, January 1956.

The changes in liver glucose-6-phosphatase activity in rat liver slices after the injection or removal of hormones known to influence carbohydrate metabolism was investigated. The activity of glucose-6-phosphatase per gram of wet liver was found to be increased over normal in fasting and alloxan-diabetic rats. Diabetic-adrenalectomized rats had normal liver glucose-6-phosphatase, whereas adrenal cortical hormones tended to increase liver phosphatase. The time required to change the activity of liver glucose-6-phosphatase was determined in diabetic rats injected with insulin and adrenalectomized-diabetic rats injected with adrenal cortical hormones. Six to twelve hours were required before hormone-induced changes in liver glucose-6-phosphatase activity were observed.

The role of glucose-6-phosphatase in diabetes was investigated. It was found that the increased gluconeogenesis and decreased fatty acid synthesis characteristic of diabetic liver metabolism precede any observed changes in liver glucose-6-phosphatase activity.

Adrenal cortical hormones appeared to act within two hours of injection to alter pyruvate metabolism in liver slices from adrenalectomized-diabetic rats. This is contrasted with the observed twelve-to-twenty-four hour delay in changes in pyruvate metabolism, following insulin injection into alloxan-diabetic rats. Glucose-6-phosphatase activity appeared to influence the relative per cent of glucose-6-phosphate converted to glucose and glycogen.

Ashworth, M. A.; and Haist, R. E. (Dept. of Physiol., Univ. of Toronto, Toronto, Ont., Canada): SOME EFFECTS OF BZ-55 (CARBUTAMIDE) ON THE GROWTH OF THE ISLETS OF LANGERHANS. Canad. M. A. J. 74:975-76, June 15, 1956.

The administration of BZ-55 by mouth to rats for a period of three to five weeks led to a significant increase in islet tissue as compared with paired-fed control animals.

Baker, Roger D. (Dept. of Pathology, Duke Univ. Sch. of Med., V.A. Hosp., Durham, N.C.): PULMONARY MUCORMYCOSIS. Am. J. Path. *32*:287-314, March-April 1956.

Diabetes mellitus was an antecedent disease in four out of ten of the cases of pulmonary mucormycosis. Diabetes has also been an important antecedent disease in cases of the cerebral form of mucormycosis. This predisposition to cerebral mucormycosis recently has been demonstrated experimentally in alloxan-induced diabetes in rabbits given spores of *Rhizopus* intranasally. Diabetes predisposes to many infections, and mucormycosis appears to be no exception.

Bangle, Raymond, Jr. (Hosp. of the Good Samaritan and Dept. of Pathology, Univ. of Southern California Sch. of Med., Los Angeles, Calif.): FACTORS INFLUENCING THE STAINING OF BETA-CELL GRANULES IN PANCREATIC ISLETS WITH VARIOUS BASIC DYES, INCLUDING PARALDEHYDE-FUCHSIN. Am. J. Path. *32*:349-62, March-April 1956.

The author found that pancreatic beta-cell granules, after oxidation or bromination, could be stained rapidly and selectively not only with paraldehyde-fuchsin but also with other basic dyes. This article deals principally with such staining reactions, with particular reference to factors that influence them. The staining methods also were applied to purified insulin crystals to determine whether any similarity exists between the staining of beta-cell granules and that of purified insulin. From the studies dealing with the staining and solubility properties of purified insulin crystals, as compared with those properties of pancreatic beta-cell granules, it is concluded that the granules do not represent stored insulin.

Beaser, Samuel B. (Harvard Med. Sch. and Beth Israel Hosp., Boston, Mass.): DIABETES MELLITUS. New England J. Med. *255*:173-80, July 26, 1956, and *255*:223-31, Aug. 2, 1956.

A review article on biochemistry and physiology, insulin and its metabolism, endocrine effects, pathology and pathogenesis, diagnosis, clinical diabetes, therapy, insulin and hypoglycemic sulfonamides, pregnancy and diabetes, and complications.

Beaton, John R.; and Goodwin, M. E. (Dept. of Pub. Health and Nutrition, Univ. of Toronto, Toronto, Canada): STUDIES ON THE EFFECT OF VITAMIN B_6 DEPRIVATION ON CARBOHYDRATE METABOLISM IN THE RAT. Canad. J. Biochem. & Physiol. *32*:684-88, November 1954.

Within five days after vitamin B_6 restriction, Wistar rats of both sexes have significantly lower levels of fasting blood sugar and of liver glycogen than pair-fed controls. After twenty-one days of deprivation, these differences are more marked and are accompanied by significantly lowered fasting blood levels of pyruvic acid and lactic acid. Lactic acid dehydrogenase activity measured in vitro was lowered significantly in the vitamin-B_6-deprived animals.

Beatty, Clarissa H.; and Peterson, Ruth D. (Dept. of Biochemistry, Univ. of Oregon Med. Sch., Portland, Ore.): COMPARISON OF URINARY EXCRETION OF KETONE BODIES, NON-PROTEIN NITROGEN, CITRIC ACID AND GLUCOSE IN ALLOXAN DIABETIC AND DEPANCREATIZED RATS. Am. J. Physiol. *183*:325-30, November 1955.

A comparison was made of urinary ketone body, nonprotein nitrogen, and citric acid excretions in alloxan-diabetic and depancreatized rats. Two groups of diabetics were selected with urinary glucose excretions at similar levels to minimize possible effects of glucose per se and in an effort to compare animals with similar degrees of diabetes. Under the conditions of these experiments, the alloxan-diabetic series exhibited less ketonuria than did the depancreatized group. No difference was demonstrated in the urinary excretion of nonprotein nitrogen or citric acid for the two groups of diabetic animals.

Beigelman, P. M.; Goetz, F. C.; Antoniades, H. N.; and Thorn, G. W. (Dept. of Med., Harvard Med. Sch., and Peter Bent Brigham Hosp., Boston; and Dept. of Biophys. Chem., Harvard Univ.): INSULIN-LIKE ACTIVITY OF HUMAN PLASMA CONSTITUENTS. I. DESCRIPTION AND EVALUATION OF BIOLOGIC ASSAY FOR INSULIN-LIKE ACTIVITY. Metabolism *5*:35-43, January 1956.

Hypophysectomy of previously alloxanized rats yields a high proportion of animals which may be employed one or more times in many instances for assay. The animals were used for assay of small quantities of insulin by utilizing the blood glucose increment which results from gavage with 300 mg. of dextrin.

Beigelman, P. M.; Antoniades, H. N.; Goetz, F. C.; Renold, A. E.; Oncley, J. L.; and Thorn, G. W. (Dept. of Med., Harvard Med. Sch., and Peter Bent Brigham Hosp., Boston; and Dept. of Biophys. Chem., Harvard Univ., Cambridge, Mass.): INSULIN-LIKE ACTIVITY OF HUMAN PLASMA CONSTITUENTS. II. BIOLOGIC ASSAY OF HUMAN PLASMA FRACTIONS FOR INSULIN-LIKE ACTIVITY. Metabolism *5*:44-50, January 1956.

Pooled human plasma protein and lipoprotein fractions were tested in hypophysectomized-alloxinated rats for evidence of insulin activity. Such activity seemed to be associated with β-globulins and lipoproteins which occur in Fractions PGP and II + III. More definite evaluation of insulin-active constituents has not been completed.

Bencosme, Sergio A. (Dept. of Path., Queen's University, Kingston, Ontario, Canada): DIFFICULTIES IN ASSESSING RELATION OF GLUCAGON TO ALPHA CELLS. Rev. canad. biol. *14*:175-83, December 1955.

In a study involving ninety-two rabbits, no appreciable morphologic alteration could be demonstrated in the cytology of the alpha cells following a single intravenous or multiple subcutaneous injections of cobalt chloride, even when lethal doses were used. There was no discernible decrease in the number of alpha cells in cobalt-injected animals relative to noninjected controls. Changes in alpha cells simulating necrosis were observed only in animals which had been found dead following injection of cobalt chloride.

In a parallel study involving forty-one guinea pigs, the lesions described by Van Campenhout *et al.* (*Ann. endocrinol. 15*:89, 1954) in the alpha cells of the cobalt-treated guinea pig were fully confirmed.

Berson, Solomon A.; Yalow, Rosalyn S.; Bauman, Arthur; Rothschild, Marcus A.; and Newerly, Katharina (Radioisotope Serv., V. A. Hosp., Bronx, N. Y.): INSULIN-I^{131} METABOLISM IN HUMAN SUBJECTS: DEMONSTRATION OF INSULIN BINDING GLOBULIN IN THE CIRCULATION OF INSULIN TREATED SUBJECTS. J. Clin. Invest. 35:170-90, February 1956.

Following intravenous administration of I^{131}-labeled insulin to human subjects, the time course of radioactivity was studied by chemical and electrophoretic methods. During the trace labeling of crystalline insulin with I^{131}, some of the insulin was altered in an unknown fashion, so that small but variable fractions of the radioactive material became bound to the serum proteins. The radioactivity bound to serum proteins disappeared from plasma much more slowly than unaltered insulin-I^{131}, so that within a short time following intravenous administration, most of the protein-precipitable radioactivity in plasma was not insulin-I^{131}.

During paper electrophoresis of plasma containing insulin-I^{131}, the labeled insulin was adsorbed to the paper at the site of application; this permitted separation from plasma-protein-bound radioactivity. The half time of disappearance from plasma-adsorbed radioactivity (insulin-I^{131}) after distribution in body fluids was approximately forty minutes, which was considered to be in good agreement with the rate of degradation of insulin-I^{131} as estimated from the rate of disappearance of nonprecipitable radioactivity in the plasma.

In subjects treated with insulin for some months to several years, the disappearance of insulin-I^{131} from plasma was found to be much slower than in subjects never treated with insulin or treated with insulin for less than two or three months. This persistence of relatively high concentrations of insulin-I^{131} in the plasma of insulin-treated subjects was shown to be due to binding of insulin-I^{131} by an acquired globulin which satisfied the criteria for antibody. The "insulin-transporting antibody" complex migrated in the front running and globulin region on paper or starch block electrophoresis at *p*H 7.3 or 8.6. The binding of insulin to circulating globulin in these patients was confirmed by ultra-centrifugation studies, in which it was observed that insulin-I^{131} in the serum of insulin-treated subjects sedimented with the globulins, but in the serum of control subjects it sedimented at a slower rate than serum albumin.

Best, Charles H. (Dept. of Physiol. and Banting & Best Dept. of Med. Res., Univ. of Toronto, Toronto, Ont., Canada): INSULIN ADJUVANTS OR SUBSTITUTES. Canad. M. A. J. 74: 957-60, June 15, 1956.

As an introduction to a series of papers on experimental and clinical results with BZ-55, Dr. Best reviews the possible modes of action which the oral sulfonylureas might have. The June 15 issue of the *Canadian Medical Association Journal* is almost entirely devoted to this series of papers.

Biran, S. (Jaffa, Israel): ATTEMPT AT A THEORY OF DIABETES MELLITUS. Helvet med. acta 22:576-606, December 1955.

Certain hypothetical assumptions are made concerning a tissue factor which influences the secretion of insulin and anterior pituitary as well as adrenal hormones. In the normal individual, insulin and the anti-insulin hormones are synergistic; the former accelerates glucose uptake of the peripheral tissues, the latter favors the supply of sufficient glucose by gluconeogenesis and glycogenolysis. Diabetes due to insufficient insulin production is explained as the attempt of the organism to compensate a primary interference with the oxidation of carbohydrates in the musculature. Diabetes due to pituitary hyperfunction is described as a shifting of the carbohydrate supplies from their depots to the peripheral tissues. (German)

Bogoch, A.; and McIntosh, H. W. (Clin. Invest. Unit. Shaughnessy Hosp., and Dept. of Med., Univ. of British Columbia, Vancouver, B. C., Canada): THE EFFECTS OF GLUCAGON ON CARBOHYDRATE METABOLISM IN PATIENTS WITH DIABETES MELLITUS. Canad. M. A. J. 74:875-81, June 1, 1956.

Seven male patients with onset of diabetes at maturity were studied with regard to the effect on the blood sugar of glucagon administered in the fasting state with and without insulin. A significant rise in blood sugar occurred when previous control of the diabetes was good. The hypoglycemic effect of insulin was altered in some patients. The degree of previous control of diabetes may determine the degree of hypoglycemic response; whether the diabetes is stable or unstable may not be significant. No correlation was found between the response to glucagon and such factors as the duration of diabetes, obesity, exogenous insulin requirement, or hepatic dysfunction. Unchanging blood lactic acid levels suggested that muscle glycogen was not involved in the organism's response to glucagon.

Bradley, R. F.; and Bryfogle, J. W. (Joslin Clin. and New England Deaconess Hosp., Boston, Mass.): SURVIVAL OF DIABETIC PATIENTS AFTER MYOCARDIAL INFARCTION. Am. J. Med. 20:207-16, February 1956.

Preliminary observations concerning the incidence of coronary artery disease in a large sample of hospitalized diabetic patients revealed an incidence of over 40 per cent. A series of 102 hospital cases, in whom a diagnosis

of coronary thrombosis was established by serial electrocardiograms or autopsy findings or both, was analyzed and followed until the patient's death or until completion of the survey. The studies disclosed that the presence of diabetes was associated with a high mortality from acute myocardial infarction: 60.8 per cent following all attacks and 57.8 per cent after the first attack. Thus, the diabetic with acute myocardial infarction appears to have a prognosis similar to that of poor risks from the general population. The high incidence of and mortality from myocardial infarction in diabetic women contributed appreciably to the over-all poor prognosis. That diabetes per se played a major part in early mortality, particularly as a result of its effect upon women, was shown by the 60 per cent early fatality rate for the series of women who did not have angina, hypertension, obesity, heart failure, or previous myocardial infarction. In contrast, an early mortality of only 8.3 per cent was found for men in whom these factors were absent.

Late survival of diabetic patients after the initial attack of myocardial infarction was also decreased; fewer than 20 per cent lived five years and only 3.6 per cent for ten years. Early death occurred in all of the eleven diabetic subjects having marked hyperglycemia and acidosis with or without ketosis. Although each experienced "shock," it could not be shown that changes in carbohydrate metabolism were directly related to the presence of shock or to histologic changes in the liver at autopsy.

Bradley, Robert F.; Sagild, Uffe; and Schertenleib, Fredy E. (Joslin Clin., New England Deaconess Hosp., Boston, Mass.): DIABETES MELLITUS AND LIVER FUNCTION. New England J. M. 253:454-58, Sept. 15, 1955.

With a battery of liver-function procedures in 118 diabetic patients with no unrelated liver disease, acute illness, or marked degrees of poor diabetic control, a total of sixteen persons (14.4 per cent) gave abnormal findings on the basis of one or more tests and only six (5.4 per cent) by two or more tests. The most sensitive of the procedures used was the bromsulfalein test, which gave the only abnormal result in nine persons. With the exception of one patient with a bromsulfalein retention of 6 per cent, fifteen patients with diabetes of more than 20 years' duration had completely negative liver-function tests. Such a low prevalence of abnormal liver function indicates that significant liver disease occurs rarely as a result merely of the presence of diabetes mellitus. From these results and the analysis of previous studies of the liver in diabetes, it can be strongly affirmed that poor control of diabetes or some other condition affecting the liver should be suspected in the presence of abnormal liver function or hepatomegaly or both.

Brown, Edward E. (25 N. Main St., Ashland, Ore.): INFECTIOUS ORIGIN OF JUVENILE DIABETES. Arch. Pediat. 73:191-98, June 1956.

The author contends that the most common cause of diabetes in children is a systemic infection which injures the islands of Langerhans and that the diabetic state is often perpetuated by repeated upper respiratory infections and chronic sinusitis. Blood-borne bacterial toxins probably prevent regeneration of the injured pancreas.

Brückner, R. (Basel, Switzerland): VASCULAR IMPAIRMENT OF VISION, ITS DIAGNOSIS AND TREATMENT. Schweiz. med. Wchnschr. 86:208-14, Feb. 25, 1956.

Review of the various vascular disorders which may lead to impairment of vision and discussion of their treatment. The author stresses the importance of good diabetic control to prevent or at least postpone diabetic retinopathy; and he quotes in detail a case to prove the superiority of good over poor antidiabetic therapy in a patient with a long history of recurrent vitreous opacities.

Campbell, James (Dept. of Physiol., Univ. of Toronto, Toronto, Ont., Canada): THE ACTION OF BZ-55 IN DOGS. PART II. OBSERVATIONS OF DEPANCREATIZED AND METAHYPOPHYSEAL DIABETIC DOGS. Canad. M. A. J. 74:962-65, June 15, 1956.

The administration of BZ-55 to diabetic dogs receiving insulin reduced fasting blood sugar, blood sugar variations during the day, and insulin requirement. These effects were more noticeable in a depancreatized dog than in a pituitary diabetic dog. On withdrawal of insulin, BZ-55 did not prevent glycosuria in the pituitary diabetic dog or the onset of signs and symptoms of ketoacidosis in the depancreatized dog. At the end of the experiment the depancreatized dog showed increased BSP retention; enlarged liver, kidneys, and adrenals; and anemia. The cause was not determined.

Clarke, D. W.; Davidson, M.; Schönbaum, E.; and Senman, H. (Dept. of Physiol., Univ. of Toronto, Toronto, Ont., Canada): SOME IN VITRO STUDIES WITH BZ-55. Canad. M. A. J. 74:966-68, June 15, 1956.

BZ-55 in vitro reduced glucose production by liver slices, an effect abolished by insulin and/or glucagon. Studies of oxygen uptake by rabbit liver slices revealed that pyruvate increases and BZ-55, in the absence of pyruvate, decreases oxygen uptake. This suggests that BZ-55 inhibits oxidation of endogenous substrates rather than of added pyruvate. Various prior treatments of the

animals also altered results. Cytochrome oxidase of rat liver homogenates was inhibited by BZ-55. Glucose uptake of rat diaphragm was decreased by BZ-55, but this effect was abolished by insulin, which gave an apparent increased insulin effect. Significant differences in glycogen synthesis were not noted, though the trend of the figures paralleled those for glucose uptake.

Clinico-pathologic Conference (Washington Univ. Sch. of Med.): ACROMEGALY, DIABETES, HYPERMETABOLISM, PROTEINURIA AND HEART FAILURE. Am. J. Med. 20:133-44, January 1956.

Presentation of case with clinical and pathological discussion.

Cochrane, W. A.; Payne, W. W.; Simpkiss, M. J.; and Woolf, L. I. (Hosp. for Sick Children, Great Ormond St., London, W.C. 1, England): FAMILIAL HYPOGLYCEMIA PRECIPITATION BY AMINO ACIDS. J. Clin. Invest. 35:411-22, April 1956.

The authors report that protein, leucine, or isovaleric acid, fed to three members of a family with spontaneous idiopathic hypoglycemia, caused a marked fall in the fasting true blood sugar level. They had a similar effect in a fourth child with hypoglycemia due to islet-cell hyperplasia but no effect in normal fasting individuals. In another case of spontaneous idiopathic hypoglycemia, casein had a less marked effect. High-protein foods produced more fits and lower blood sugar values in the affected family than did a low-protein diet. The nonsugar reducing level was significantly outside the normal range of some blood samples from these patients, so that, according to the authors, the apparent blood sugar level can be very misleading. The nonsugar reducing level fell nearly as fast as the true blood sugar level on feeding leucine or casein. A casein test meal is advocated as a means of differentiating this type of hypoglycemia.

Cohen, Alan S. (Thorndike Memorial Lab., Boston City Hosp., Dept. of Med., Harvard Med. Sch., Boston, Mass.): DIFFERENTIAL DIAGNOSIS OF SALICYLATE INTOXICATION AND DIABETIC ACIDOSIS: REPORT OF A CASE AND REVIEW OF THE CLINICAL, LABORATORY AND PATHOGENETIC FEATURES. New England J. Med. *254*: 457-61, March 8, 1956.

The polydipsia, polyuria, hyperpnea, nausea, and vomiting often associated with salicylate intoxication have caused it to be misdiagnosed as diabetic acidosis. The occurrence of positive urinary acetone and reducing tests, combined with occasional elevations of the blood sugar level and depression of the carbon dioxide combining power, has made differentiation of these two states even more confusing. However, clinically, the presence of tinnitus, muscular irritability, and petechiae, combined with the lack of dehydration and hepatomegaly, points to a diagnosis of salicylate intoxication. This diagnosis may be confirmed by a positive urine ferric chloride test (after boiling of the urine) and an elevation of the blood salicylate. A case exemplifying these difficulties is presented, and the pertinent literature is reviewed. The specific biochemical abnormalities causing the hyperglycemia, acidosis, glycosuria, and ketonuria are individually discussed. Despite the abnormalities that cause salicylate intoxication to mimic diabetic acidosis, the former state has many pharmacologic accompaniments that work in an opposing direction, actually creating a glucose demand in the body. The many biochemical and experimental data that have accumulated on these drugs have not yet fully explained their complex interrelation with carbohydrate metabolism.

Colwell, Arthur R.; and Weiger, Robert W. (Depts. of Med., Northwestern Univ. Med. Sch. and Passavant Memorial Hosp., Chicago, Ill.): INHIBITION OF INSULIN ACTION BY SERUM GAMMA GLOBULIN. J. Lab. & Clin. Med. 47:844-61, June 1956.

A seven-month study of a man with fatal hemochromatosis and severe, labile diabetes mellitus is reported. There was extreme resistance to insulin, with the requirement increasing progressively to 11,400 units daily. This was associated with hypergammaglobulinemia. Both phenomena were reduced almost to normal by corticotropin administration. Seventeen serial blood serums, obtained at intervals before and after corticotropin, were studied biologically and electrophoretically. When mixed with convulsive and/or lethal doses of insulin and injected into mice, they showed marked insulin-inhibiting properties, and the resistance of the patient and gamma globulin values were high. On reversal of these conditions, the insulin-inhibiting titers of the serums decreased concurrently and correspondingly. The insulin-inhibitor was nondialyzable and stable at refrigerator temperatures. It is concluded that the serum gamma globulin of this patient contained an unknown substance which inhibited insulin effect up to the point of excessive dosage. Inhibition seemed to occur whether the anti-insulin substance was supplied in vitro or in vivo. The suggestion is offered that a fundamental mechanism might be revealed by further study of phenomena such as these. Resistance to insulin in this form might be merely an exaggerated form of a much less readily apparent but similar mechanism in diabetes with normal sensitivity to insulin.

Committee on Diabetes, Massachusetts Medical Society (Boston, Mass.): SURGICAL LESIONS OF DIABETIC FEET. New England J. Med. 253:685-88, Oct. 20, 1955.

A survey article reviewing surgical lesions of diabetic feet in several Boston hospitals.

Conn, Jerome W.; and Seltzer, Holbrooke S. (Div. of Endocrinology and Metabolism, Univ. of Michigan Med. Sch., Ann Arbor, Mich.): SPONTANEOUS HYPOGLYCEMIA. Am. J. Med. *19*:460-78, September 1955.

The term "spontaneous hypoglycemia" is defined and the symptomatic manifestations described. A comprehensive classification of spontaneous hypoglycemia based upon etiologic factors is presented, and determination of etiology in the individual case is discussed. The three most frequent categories—functional hyperinsulinism, organic hyperinsulinism, and hepatogenic hypoglycemia—are next considered in detail, with illustrative case reports. A discussion of some of the rarer causes of spontaneous hypoglycemia concludes the presentation.

Cornblath, Marvin (Sinai Hosp. of Baltimore, The Harriet Lane Home, Johns Hopkins Hosp., and the Dept. of Pediat., Johns Hopkins Med. Sch., Baltimore, Md.): REACTIVATION OF RABBIT LIVER PHOSPHORYLASE BY EPINEPHRINE, GLUCAGON AND EPHEDRINE. Am. J. Physiol. *183*:240-44, November 1955.

The liberation of inorganic phosphorus by homogenates was shown to be a measure of phosphorylase reactivation in rabbit liver slices by epinephrine, glucagon, and ephedrine. In increasing concentrations, epinephrine and glucagon produced an almost linear increase in phosphorylase activity. Ephedrine and glucagon are additive in their effect on phosphorylase, whereas ephedrine and epinephrine are not. These data preclude either identical or entirely different mechanisms of action for these hormones.

Curran, George L.; and Costello, Richard L. (Dept. of Med., Univ. of Kansas Sch. of Med., Kansas City, Kan.): REDUCTION OF EXCESS CHOLESTEROL IN THE RABBIT AORTA BY INHIBITION OF ENDOGENOUS CHOLESTEROL SYNTHESIS. J. Exper. Med. *103*:49-56, January 1956.

Hepatic cholesterol synthesis in rabbits, as measured by the incorporation of C^{14}-labeled acetate, was found to be inhibited by addition of nontoxic amounts of vanadium, as vanadyl sulfate (0.05 per cent $VOSO_4 \cdot 2H_2O$) to the diet. This diet reduced excess aortic cholesterol in cholesterol-prefed rabbits when fed during the six weeks immediately following a four-week period of cholesterol feeding.

Davies, J. (Dept. of Anat., State Univ. of Iowa, Iowa City, Ia.): PERMEABILITY OF THE RABBIT PLACENTA TO GLUCOSE AND FRUCTOSE. Am. J. Physiol. *181*:532-38, June 1955.

Pregnant rabbits at different stages of gestation, from the seventeenth to the last day, have been infused intravenously with glucose or fructose for periods of one to two hours. Fetal blood levels of glucose and fructose have been studied during the infusion in anesthetized animals and at the end of the infusion in unanesthetized animals. Gradients from maternal to fetal blood were higher in the case of fructose (mean of 641 mg. per cent) than in the case of glucose (mean of 198 mg. per cent) at the end of a one-hour infusion period. When plotted at half-hourly intervals, the fetal blood curve rose rapidly and ran parallel to the maternal curve during an infusion of glucose. During the infusion of fructose, the fetal fructose curve remained low and showed a steady rise throughout the infusion period which continued into the postinfusion period. Homogenates of whole fetal body and of fetal placenta at the end of infusions of fructose showed an excess of fructose in the fetal placenta as compared with the fetal body. No such discrepancy between fetal and placental glucose was found following the infusion of glucose. From the above findings, it was concluded that a relative "placental barrier" to fructose exists in the rabbit as contrasted with glucose. In all probability, this barrier exists in the reverse direction also. It is present at all stages of gestation after the seventeenth day. Small amounts of fructose were demonstrated in the fetal blood of normal rabbits. This was significantly increased following a two-hour period of maternal hyperglycemia. Phlorhizin was without demonstrable effect on the gradients from maternal to fetal blood in hyperglycemic animals. The conclusion was reached that "simple diffusion" is inadequate to account for the placental transmission of the hexoses, glucose and fructose; an "active process" must be invoked, the nature of which remains unknown.

Deiss, W. P., Jr.; and Willard, R. F. (Dept. of Med. and Biochem., Duke Univ. Sch. of Med., and V. A. Hosp., Durham, N. C.): SERUM PROTEIN-BOUND GLUCOSAMINE AND GALACTOSAMINE. Am. J. Med. *20*:945, June 1956. (Abstract of a paper presented at the Tenth Annual Meeting of the Southern Society for Clinical Research, New Orleans, La., Jan 21, 1956.)

The authors investigated the possibility of qualitative differences in the serum mucoprotein of a variety of clinical diseases in which elevation of serum mucoprotein and protein-bound carbohydrate have been reported. The hexosamines, characteristic constituents of these carbohydrate-containing proteins, were fractionated on ion exchange columns; the glucosamine/galactosamine ratio was taken as a measure of qualitative differences in carbohydrate-bound protein. In all the pathological serums tested three subjects with rheumatoid arthritis,

one with disseminated lupus erythematosus, two with Buerger's disease, and two diabetics with Kimmelstiel-Wilson syndrome), the glucosamine/galactosamine ratio was found to resemble very closely that found in normal serum. From this, the authors conclude that there was no qualitative difference in protein-bound hexosamine in the limited series studied.

Dische, Zacharias; Borenfreund, Ellen; and Zelmenis, G. (New York, N. Y.): PROTEINS AND PROTEIN SYNTHESIS IN RAT LENSES WITH GALACTOSE CATARACT. A.M.A. Arch. Ophth. 55:633-42, May 1956.

Based on the authors' experiments, the lenses of rats on a galactose diet show up to 100 per cent inhibition of the net synthesis of soluble proteins as compared with controls on a normal diet. This inhibition is accompanied by an accumulation of the protein, which precipitates after oxidation with ferricyanide. The formation of albuminoid in rat lenses on a galactose diet is inhibited no more than 20 per cent. This inhibition is smaller than could be expected on the assumption that the formation of albuminoid from soluble proteins follows a first-order reaction. The possible significance of these findings in the pathogenesis of cataract is discussed.

Dole, Vincent P. (Rockefeller Inst. for Med. Research, New York, N. Y.): A RELATION BETWEEN NON-ESTERIFIED FATTY ACIDS IN PLASMA AND THE METABOLISM OF GLUCOSE. J. Clin. Invest. 35:150-54, February 1956.

The concentration of nonesterified fatty acids in plasma was found to increase with fasting, to decrease after a mixed meal, oral glucose (50 gm.), or injected insulin (0.1 unit per kg.), and to rise markedly after injection of epinephrine (0.5 mg.). Corn oil, on the other hand, failed to cause any change, even when enough was taken to produce gross lipemia. The fasting levels of NEFA were normal in three men with chronic elevation of total plasma lipids, neutral fat, cholesterol, and phospholipids. A new method for determination of NEFA, said to be more rapid and sensitive than previous technics, is described.

Editorial (Toronto, Ont., Canada): ANOTHER ORAL DRUG FOR DIABETES. Canad. M. A. J. 75:224-25, Aug. 1, 1956.

A review of the symposium on D-860 (Orinase) in the *Deutsche medizinische Wochenschrift,* May 25 and June 1, 1956.

Elder, T. David; and Baker, Roger Denio (Dept. of Path., Duke Univ. Sch. of Med. and the V. A. Hosp., Durham, N. C.): PULMONARY MUCORMYCOSIS IN RABBITS WITH ALLOXAN DIABETES: INCREASED INVASIVENESS OF FUNGUS DURING ACUTE TOXIC PHASE OF DIABETES. A.M.A. Arch. Path. 61:159-68, February 1956.

The authors investigated the susceptibility of rabbits, in the acute toxic phase of alloxan diabetes, to spores of *Rhizopus arrhizus.* Ulcerative bronchitis and extensive pneumonia with vascular invasion and thrombosis resulted in death of the rabbits in one to three days, depending on the size of the infecting dose of spores. Nondiabetic control rabbits and rabbits in the chronic phase of alloxan diabetes showed only a mild acute-pneumonia and giant-cell response without hyphal proliferation of the organism and without vascular thrombosis. The reaction seen in the acute phase of alloxan-diabetic rabbits resembled the fulminating pulmonary lesions of human mucormycosis (presumably due to *Rhizopus*) which develop in unregulated and ketotic patients with diabetes mellitus. The increased susceptibility to *Rhizopus* infection in the acute phase of alloxan diabetes does not appear to be due to hyperglycemia, failure of inflammatory response to the infection, or lowered body temperature. Loss of phagocytic ability of macrophages and giant cells, ketosis, devitalization of tissues, and changes in leucocyte metabolism are suggested as possible causes.

Epstein, Franklin H.; and Zupa, Vito Joseph (Dept. of Internal Med., Yale Univ. Sch. of Med., New Haven, Conn.): CLINICAL CORRELATES OF THE KIMMELSTIEL-WILSON LESION. New England J. Med. 2:896-900, May 10, 1956.

The clinical courses of thirty-seven diabetic patients with nodular intercapillary glomerulosclerosis and of thirty-seven without this lesion are reviewed. The age and sex distribution was similar in the two groups. Persistent albuminuria, hypoalbuminemia, hypertension, neuropathy, retinopathy, cardiac failure and renal decompensation were frequent among patients with intercapillary glomerulosclerosis. Nodular intercapillary glomerulosclerosis was always associated with sclerosis of large and small renal vessels and frequently with pyelonephritis. Intercapillary glomerulosclerosis was found in patients with all levels of basal insulin requirement. In only six patients with this lesion was a decreased requirement of insulin noted terminally. Diabetic acidosis occurred at least once in 14 of 37 patients with nodular glomerulosclerosis. The present study does not support the view that a specific or unique type of diabetes, characterized by infrequent episodes of acidosis and a decreasing requirement of insulin, is associated with the nodular glomerular lesion of Kimmelstiel and Wilson.

Evans, John A.; and Ross, Wayne D. (New York Hosp., New York 21, N. Y.): RENAL PAPILLARY NECROSIS. Radiology *66*:502-08, April 1956.

A case of renal papillary necrosis was presented with pathological and radiological discussion and illustration.

Farquhar, James W. (Dept. of Child Life and Health, Univ. of Edinburgh, Scotland): THE SIGNIFICANCE OF HYPOGLYCAEMIA IN THE NEWBORN INFANT OF THE DIABETIC WOMAN. Arch. Dis. Childhood. *31*:203-11, June 1956.

Confirmatory evidence is offered that the blood sugar level falls more profoundly and more rapidly in the infant of the diabetic mother than in the offspring of the normal woman. It is shown that there is no relationship between the development of a morbid neonatal course and the blood sugar level at the time or the extent and rapidity of the fall. It is shown also that there is no relationship between the degree of hypoglycemia or the gradient of the change in levels and abnormal incidents later in the first two weeks of life. It is probable that there is no relationship between the blood sugar changes and subnormal intelligence in later childhood. The administration of glucose may be dangerous and, at the least, may serve to postpone the establishment of the correct diagnosis in abnormal infants.

Felts, J. M.; Doell, Ruth G.; and Chaikoff, I. L. (Dept. of Physiol., Univ. of California Sch. of Med., Berkeley, Calif.): THE EFFECT OF INSULIN ON THE PATHWAYS OF CONVERSION OF GLUCOSE TO FATTY ACIDS IN THE LIVER. J. Biol. Chem. *219*:473-78, March 1956.

The authors compared the conversion of the C^{14} of glucose-1-C^{14} and glucose-6-C^{14} to CO_2 and fatty acids in livers of normal rats, alloxan-diabetic rats, and insulin-treated, alloxan-diabetic rats. It was found that injection of insulin in the diabetic rats increased the $C^{14}O_2$ recoveries from glucose-1-C^{14} to a much greater extent than it did from glucose-6-C^{14}. The hormone treatments increased the incorporation of the C^{14} of both glucose-1-C^{14} and glucose-6-C^{14} into fatty acids by the diabetic liver, but the effect was much more pronounced on carbon 6 than on carbon 1.

The fractions of the fatty acid-C^{14} that arose via the Embden-Meyerhof and alternative pathways were estimated from the relative conversions of carbons 1 and 6 of glucose to fatty acids. In this calculation, it is assumed that the first carbon of glucose is incorporated into fatty acid solely by the Embden-Meyerhof pathway, whereas carbon 6 is converted to fatty acid both by the latter and by the phosphogluconate oxidation pathway. The injection of insulin in the diabetic rat resulted in a three-fold increase in the fraction of the fatty acid C^{14} that arose via the phosphogluconate oxidation pathway. The microatoms of carbon 6 of *added* glucose converted to fatty acids by liver slices were also calculated. Insulin injections for two days resulted in an increase of about seventy-fold in conversion via the Embden-Meyerhof pathway and of about 375-fold in the phosphogluconate pathway.

Ferner, H.; and Runge W. (Inst. of Anat., Univ. of Hamburg, Germany): MORPHOLOGICAL STUDIES OF THE ACTION OF N_1-SULFANILYL-N_2-N-BUTYLCARBAMIDE ON THE ISLET CELLS IN RABBITS AND RATS. Arzneimittel-Forsch. *5*:256-60, May 1956.

Application of large doses of N_1-sulfanilyl-N_2-n-butylcarbamide (BZ-55) in rats and rabbits induces selective damage to part of the alpha cells of the insular tissue. The extent of the damage is markedly less than after p-aminobenzene-sulfonamideisoprophylthiazol or Synthalin A. No degenerative changes are observed in the β cells and in the exocrine parenchyma. The liver and kidneys also show no damage. The depression of blood sugar level observed in diabetics and normal human beings after BZ-55 appears to be related to suppression and part-inhibition of glucagon production. (German)

Fisher, Peter (Seattle, Wash.): INSULIN SENSITIVITY. Northwest Med. *55*:657-58, June 1956.

Generalized insulin sensitivity is considered to be rare; it occurs in about one in a thousand diabetics who use insulin. Some degree of local reaction at the site of injection is relatively common, occurring in 20 to 80 per cent of all diabetics when they first start using insulin. Severe local reactions requiring desensitization are uncommon; most patients automatically desensitize themselves during the first few weeks of insulin therapy. Local reactions include redness, tenderness, induration, urticaria, hematoma, and pruritus. Changing the brand of insulin may be all that is needed, for different brands may have different allergenic properties. Sensitivity may result from either the beef or porcine protein alone. Commercial insulins are combinations of both of these, but insulins containing the single protein are available for use in sensitivity problems. Occasionally, sensitivity results from a product added to the insulin either to preserve it or to prolong its action. A change to regular insulin may eliminate these factors. Crystalline insulin is even less allergenic than regular insulin. Recent reports suggest that Lente insulin may have lower allergenic properties than previous insulins and is worth trying.

Occasionally, reactions depend on technic of injection. Sometimes, use of a longer needle and its insertion at right angles to the skin in order to place the insulin deeper may solve the problem. If there is a question of the reaction's resulting from trauma of the injection alone, saline can be substituted for insulin to determine if reaction still occurs. Local antiseptic agents may cause a reaction. Preparation of the skin for injection using soap and water only should be tried. Other general measures have been advocated which include use of antihistamines, ephedrine, or histamine desensitization.

Fodden, John H. (Dept. of Path., Sch. of Med., Univ. of S. D.): CYTOPATHOLOGIC EFFECTS OF COBALT ON PANCREATIC ISLETS OF MANY SPECIES: ISLANDS OF LANGERHANS AND COBALTOUS CHLORIDE. A.M.A. Arch. Path. *61*:65-75, January 1956.

Cobaltous chloride, administered to many animal species, fails to produce pancreatic alpha-cell necrobiosis of any significance. The use of radioactive cobaltous chloride and other chemical measures offers no evidence of a preferential deposition of the cobalt ion about or within the cells of the islet tissues.

Friedlich, T. L.; Ashworth, M. A.; Hawkins, Rosemary D.; and Haist, R. E. (Dept. of Physiol., Univ. of Toronto, Toronto, Ont., Canada): AN EFFECT OF BZ-55 (CARBUTAMIDE) ON THE RATE OF ABSORPTION OF GLUCOSE FROM THE GASTROINTESTINAL TRACT. Canad. M. A. J. *74*:973-74, June 15, 1956.

Intravenous administration of BZ-55 in rats three hours before glucose administration per os led to decreased absorption of glucose from the gut, as evidenced by greater residues of reducing substances in the gut of treated animals. An interesting additional finding was that the stomachs of the treated animals were fluid filled, whereas those of the control animals were essentially empty. The composition of this fluid was not known.

Frohman, Charles E.; and Orten, James M. (Dept. of Physiol. Chem., Wayne Univ. Coll. of Med., Detroit, Mich.): TRACER STUDIES OF ACIDS OF THE TRICARBOXYLIC ACID CYCLE. II. EFFECT OF FRUCTOSE AND BICARBONATE ON ACETATE METABOLISM IN LIVERS OF DIABETIC RATS. J. Biol. Chem. *220*:315-19, May 1956.

The blood sugar levels and the rate of incorporation of acetate into the acids of the tricarboxylic acid cycle were measured in the livers of normal and diabetic rats fed either glucose or fructose as the only source of carbohydrate. The effect of bicarbonate on the blood sugar levels and the rate of incorporation of acetate were also investigated. It was found that fructose had no effect on either the blood sugar levels or the incorporation of acetate in the livers of alloxanized animals. Bicarbonate also had no effect on the blood sugar levels but did increase the rate of utilization of acetate by the liver of the diabetic rat. On the basis of these results, the authors suggest that at least two reactions are blocked in the livers of alloxanized rats, one of which involves utilization of glucose and the other utilization of acetate.

Fuller, John L.; and Jacoby, George A., Jr. (Div. of Behavior Studies, R. B. Jackson Memorial Lab., Bar Harbor, Me.): CENTRAL AND SENSORY CONTROL OF FOOD INTAKE IN GENETICALLY OBESE MICE. Am. J. Physiol. *183*:279-83, November 1955.

Genetically obese mice are less able than their normal sib controls to adjust food intake adaptively when their diet is (a) diluted with cellulose, (b) made bitter, (c) enriched by fat. The difference between genotypes is attributed to differential response of the nervous system to signals arising from biological need rather than to differential food preference. Other studies have demonstrated the metabolism of the obese mouse to be aberrant, and ultimately it develops hyperglycemia; but the obese syndrome is manifest at eight weeks of age when the blood sugar levels of obese and lean sibs are similar. Therefore, there is no apparent relationship of the food control of the obese mouse to the glucostatic theory of hunger regulation.

Gershberg, Herbert; and Ralli, Elaine P. (Third (N.Y.U.) Med. Div. and the Third (N.Y.U.) Med. Div. Metabolism Clinics, Bellevue Hosp., New York, N. Y.): STUDIES ON A PATIENT WITH SEVERE HYPERINSULINISM TREATED WITH CORTISONE FOR THREE YEARS. Am. J. Med. *20*:631-37, April 1956.

Studies are presented on a 61-year-old male patient with severe hypoglycemia which responded for three years to treatment with 25 mg. of cortisone daily. The relationship between vasomotor lability and hypoglycemia is emphasized. As the patient's blood glucose level fell below 70 to 60 mg. per cent, the blood pressure and heart rate rose. When glucose was ingested, the blood pressure and heart rate fell immediately. A further decrease in blood glucose to a level of 38 to 36 mg. per cent produced hypoglycemic symptoms. The authors suggest that norepinephrine and epinephrine are released from the human adrenal medulla in response to different levels of hypoglycemia. They also suggest that mild hyperinsulinism may be suspected in an individual who shows such cardiovascular changes in relation to food.

Goodman, Daniel H. (Phoenix, Ariz.): TRUE RENAL GLYCOSURIA. Arizona Med. *13*:88-90, March 1956.

True renal glycosuria is a benign, uncommon condition, in which glucose is found in the urine at all times—even in the fasting state—and at all levels of blood sugar. There is a defect in the cells of the proximal convoluted tubules, resulting in a diminished capacity of these cells to reabsorb glucose from the glomerular filtrate without any other associated abnormality of excretory function of the kidneys. The recognition of true renal glycosuria is emphasized because it is frequently mistaken for diabetes mellitus and pseudorenal glycosuria. It is not a forerunner of diabetes. It requires no treatment except possibly during pregnancy. A typical case of true renal glycosuria is presented, and differentiation from diabetes mellitus and other forms of nondiabetic glycosuric meliturias is discussed.

Grollman, Arthur (Dept. of Exper. Med., Univ. of Texas Southwestern Med. Sch., Dallas, Tex.): DIABETES MELLITUS—PHYSIOLOGIC CONSIDERATIONS. Am. Pract. & Digest Treat. *7*:557-59, April 1956.

The author discusses the basic physiological disturbances in diabetes and discusses the complexities involved. He points out that advances in understanding basic mechanism involved in metabolism have broadened the knowledge of the functional pathology of diabetes and uncovered many problems which remain to be solved.

Hagen, Horst (Medizinischen Klinik und Diabetikerheim des Waldkrankenhauses Zeven, Hannover, Germany): DIABETES MELLITUS AND PERNICIOUS ANEMIA. München. med. Wchnschr. *98*:303-304, March 2, 1956.

Report is given on the incidence and pathogenesis of a combination of diabetes and pernicious anemia. The significance of achylia and of other features common to both diseases are pointed out. (German)

Harvey, John Collins; and De Klerk, Johan (Depts. of Med. and Urology, The Johns Hopkins Univ. and Hosp., Baltimore, Md.): THE HOUSSAY PHENOMENON IN MAN. Am. J. Med. *19*:327-36, September 1955.

The authors reviewed eleven previously recorded cases and added three of their own of the Houssay phenomenon in man. It was found that this condition, when it occurs, usually involves individuals who have had diabetes mellitus for a long time and is most often caused by infarction of the anterior lobe of the pituitary gland. One of the first effects of the anterior pituitary insufficiency was hypoglycemia, developing within twenty-four hours after the infarction occurred. The hypoglycemia was manifested by bizarre and rapidly changing neurologic signs associated with unconsciousness. These individuals manifested extreme sensitivity to administered insulin. Those surviving the acute phases of this illness began within a month or two to display the clinical manifestations of deficiencies of thyroid, adrenal, and gonadal hormones. It is emphasized that in these individuals, although the symptoms of diabetes disappeared, glycosuria decreased, and the level of blood sugar approached normal, the diabetic tendency remained. The response to the stress of intravenously administered glucose was still diabetic in type. Continual administration of insulin was required in some of the individuals.

Hausberger, F. X.; and Hausberger, B. C. (Daniel Baugh Inst. of Anat., Jefferson Med. Coll. of Philadelphia, Philadelphia, Pa.): OVER-ALL GLUCOSE UTILIZATION IN STEROID DIABETIC GUINEA PIGS. Am. J. Physiol. *183*:302-06, November 1955.

The over-all glucose utilization of guinea pigs was determined during a pre-experimental period and during the period of marked steroid diabetes produced by administration of cortisone or hydrocortisone. The amount of glucose utilized was calculated: (a) from the carbohydrate content of the food consumed, (b) from the gluconeogenesis from protein using a D/N ratio of 3.65, and (c) from the amount of glucose excreted in the control and experimental periods. All animals injected with diabetogenic doses of steroids and maintained in a healthy condition compensated the glucose loss fully by increased food intake and increased gluconeogenesis. The amount of glucose utilized during the diabetic stage was definitely not diminished.

Hawkins, Rosemary D.; Ashworth, M. A.; and Haist, R. E. (Dept. of Physiol., Univ. of Toronto, Toronto, Ont., Canada): THE EFFECT OF BZ-55 (CARBUTAMIDE) ON GLUCOSE-6-PHOSPHATASE ACTIVITY. Canad. M. A. J. *74*:972-73, June 15, 1956.

The oral administration of BZ-55 to normal rats for periods of three weeks gave a significant depression in the glucose-6-phosphatase activity of liver.

Haworth, J. C.; and McCredie, David (Children's Hosp., Sheffield, England): CHROMATOGRAPHIC SEPARATION OF REDUCING SUGARS IN THE URINES OF NEWBORN BABIES. Arch. Dis. Childhood *31*:189-90, June 1956.

The urines of fifty normal male babies were examined for reducing sugars by paper chromatography. Twenty-four babies excreted either lactose, galactose, or xylose or a combination of these sugars at some time during the first seven days of life.

Henley, Keith S.; Wiggins, Hugh S.; and Pollard, H. Marvin (Gastrointestinal Div., Dept. of Internal Med., Univ. of Michigan Med. Sch., Ann Arbor, Mich.): THE DETERMINATION OF PYRUVATE IN PLASMA. J. Lab. & Clin. Med. 47:978-80, June 1956.

A rapid enzymatic method for the determination of pyruvate in plasma is presented, which depends on the conversion of pyruvate to lactate in the presence of lactic acid dehydrogenase and diphosphopyridine nucleotide. The method is reproducible with a standard error of 3.6 per cent and has yielded a normal plasma pyruvate value of 0.69 ± 0.25 mg. per 100 ml.

Hernandez, H. H.; Chaikoff, I. L.; and Kiyasu, J. Y. (Dept. of Physiol., Univ. of California Sch. of Med., Berkeley, Calif.): ROLE OF PANCREATIC JUICE IN CHOLESTEROL ABSORPTION. Am. J. Physiol. *181*:523-26. June 1955.

A test preparation for the study of the effects of pancreatic juice and bile on cholesterol absorption is described. For this purpose rats in which both pancreatic juice and bile are kept from entering the intestinal tract by cannulating the common bile duct at its duodenal junction are used. As judged by the recovery of the C^{14} of administered C^{14}-cholesterol in thoracic-duct lymph, this preparation has lost the capacity for absorbing cholesterol. The continuous administration of pancreatic juice alone does not re-establish cholesterol absorption. The continuous administration of bile alone enables the test rat to absorb cholesterol, but at much reduced rates as compared with the control rat. In the presence of bile, pancreatic juice stimulates cholesterol absorption. Normal cholesterol absorption was obtained by the continuous dripping of both bile and pancreatic juice into the duodenums of the test rats. Homogenates prepared from the duodenums of rats in which pancreatic juice was prevented from entering the intestinal tract gradually lose the capacity for esterifying cholesterol; and by the time twenty-four hours have elapsed, the loss is almost complete. At this time, the rat has also lost the ability to absorb cholesterol.

Illingworth, Barbara; Cori, Gerty T.; and Cori, Carl F. (Dept. of Biol. Chem., Washington Univ. Sch. of Med., St. Louis, Mo.): AMYLO-1, 6-GLUCOSIDASE IN MUSCLE TISSUE IN GENERALIZED GLYCOGEN STORAGE DISEASE. J. Biol. Chem. *218*:123-29, January 1956.

The activity of the enzyme amylo-1, 6-glucosidase (debranching enzyme) was determined in skeletal and heart muscle of children. In two cases of generalized storage disease in which glycogens had abnormally short outer chains, no enzyme activity was detected. The authors postulate that the absence of this enzyme can explain the abnormal glycogen structure and the accumulation of glycogen in the tissues and that it supports the view that this is a distinct type of glycogen storage disease. In hearts and skeletal muscle obtained from three children with general storage disease in which the glycogens had outer branches of normal length, glucosidase activity was within the range found in children who did not have glycogenosis in two instances and was very low in the third.

Izzo, Joseph L. (Dept. of Med., Univ. of Rochester Sch. of Med., and the Diabetic Clin., Strong Memorial Rochester Municipal Hosp., Rochester, N. Y.): INSULIN-ZINC SUSPENSIONS: FURTHER STUDIES, WITH EMPHASIS ON LENTE INSULIN. Am. J. Med. 20:554-63, April 1956.

A mixture containing 70 per cent insulin-zinc crystals and 30 per cent amorphous insulin-zinc, referred to as "Lente" insulin, was compared with NPH insulin in six patients with unstable diabetes. The insulins were compared on the basis of their ability to control the extent of, or to influence the pattern of, variability of blood sugar response, according to a technic previously reported. No consistent tendency for one insulin to maintain intradaily or interdaily variability in blood sugar at levels higher or lower than the other was observed. In other words, no large differences in predictability of action and consistency of response between the two insulins were noted. The daily distribution of activity of the two insulins, as measured by the patterns of intradaily variability, was similar, although the action of Lente insulin was found to be slightly slower than that of NPH insulin. For this reason, it was pointed out, the two insulins may not always be interchangeable, especially in the unstable cases.

The solubility properties of amorphous insulin-zinc, insulin-zinc crystals, and mixtures of the two were studied in a standardized-serum-containing, in vitro system. A graded series of solubility curves was obtained. Amorphous insulin-zinc dissolved rapidly, whereas insulin-zinc crystals dissolved at a slow rate. The solubility curves of mixtures of the two were intermediate between these two extremes. A good correlation was observed between the relative solubility properties and relative clinical timing of the preparations studied. This suggests that it is possible to obtain a series of insulin-zinc suspensions with different durations of activity which would meet the varied timing requirements of most, if not all, patients with unstable as well as stable diabetes. The three major patterns of sugar response to successive single daily doses of any given insulin and some of the interrelationships among type of response, type

of patient, and type of insulin, together with their implications, are discussed.

Judson, Walter E.; and Hollander, William (Robert Dawson Evans Memorial Dept. of Clin. Res. & Preventive Med., Mass. Memorial Hosp.; and Dept. of Med., Boston Univ. Sch. of Med., Boston, Mass.): THE EFFECTS OF INSULIN-INDUCED HYPOGLYCEMIA IN PATIENTS WITH ANGINA PECTORIS: BEFORE AND AFTER INTRAVENOUS HEXAMETHONIUM. Am. Heart J. *52*:198-209, August 1956.

A group of eleven patients did not develop angina pectoris during eighteen episodes of experimentally induced insulin hypoglycemia. Included in the group were one patient who was maintained in insulin shock for over two hours and another who had developed semicoma and required intravenous glucose therapy. However, during the hypoglycemic state, the group frequently developed electrocardiographic alterations which were not dissimilar to those reported in normal subjects. The electrocardiographic changes consisted in broadening, flattening, and inversion of the T waves and disturbances in rhythm, such as premature beats, bigeminy, and ventricular tachycardia. These abnormalities were associated with decreases in the blood glucose and serum potassium; indeed, the changes in T waves were often not unlike those observed during other hypopotassemic states. It is unlikely that the electrocardiographic changes were caused by coronary insufficiency, since they were totally unlike those observed during a documented attack of angina pectoris. The absence of chest pain during the hypoglycemic state is added evidence that the changes in the electrocardiogram were not caused by coronary insufficiency. No convincing evidence was obtained to suggest that the alterations in the electrocardiogram were due to sympathoadrenal neural discharges secondary to the insulin-induced hypoglycemia. The failure to induce angina pectoris with insulin in the present study does not support the impression that coronary insufficiency is a frequent complication of hypoglycemia but, rather, suggests that this complication is rare.

Koenig, Virgil L.; Weiger, R. W.; and Sowinski, Raymond (Dept. Investigative Med., V.A. Res. Hosp., Depts. of Med. and Biochem., Northwestern Univ. Med. Sch., Chicago, Ill.): ELECTROPHORETIC ANALYSIS OF SERA FROM A PATIENT WITH HEMOCHROMATOSIS AND DIABETES RESISTANT TO INSULIN. J. Lab. & Clin. Med. *47*:862-68, June 1956.

The serum of a patient suffering from insulin-resistant diabetes and hemochromatosis has been analyzed electrophoretically by the moving-boundary and the paper technics. The abnormally high insulin requirement of the patient, accompanied by a high γ-globulin content of the serum, suggested insulin-inhibiting antibody formation. The γ-globulin content and the insulin requirement were decreased with ACTH treatment.

Landau, Bernard R.; Hastings, A. Baird; and Nesbett, Frances B. (Dept. of Biol. Chem., Harvard Med. Sch., Boston, Mass.): ORIGIN OF GLUCOSE AND GLYCOGEN CARBONS FORMED FROM C^{14}-LABELED PYRUVATE BY LIVERS OF NORMAL AND DIABETIC RATS. J. Biol. Chem. *214*:525-35, June 1955.

Rat liver slices were incubated with pyruvate-2-C^{14} under a variety of experimental conditions. Crystalline glucose was isolated from the glycogen formed in the liver and the glucose formed in the medium. The glucose was degraded so that the specific activity of all its carbon atoms could be determined. The distribution of activity in the glucose from the glycogen was found to be the same as that of the glucose from the medium for each incubation. With pyruvate-2-C^{14}, asymmetrical labeled glucose was obtained. The extent of the asymmetry appeared to depend on the availability of nonradioactive trioses. The distribution of activity in the glucose and glycogen formed by liver slices from normal-fed, diabetic-fed, and normal-fasted rats with pyruvate-2-C^{14} as substrate was determined. The data were interpreted to indicate that a relatively larger proportion of metabolized pyruvate is incorporated into glucose by the liver of diabetic and fasting animals than by that of normal-fed animals.

Lukens, F. D. W. (Philadelphia, Pa.): EXPERIMENTAL DIABETES AND ITS RELATION TO DIABETES MELLITUS. Am. J. Med. *19*:790-97, November 1955.

The important contributions made by the experimental production of diabetes in animals to the understanding of the naturally occurring human disorder and to further study of the disease in man are reviewed. The significance of the observations in experimental diabetes in relation to the clinical disease is discussed. An appraisal of the severity of the metabolic derangement in diabetes mellitus on the basis of multiple criteria is presented.

Mann, George V.; Teel, Katherine; Hayes, Olive; McNally, Ann; and Bruno, Dorothy (Dept. of Nutrition, Harvard Sch. of Public Health; Dept. of Med., Peter Bent Brigham Hosp., Boston, Mass.): EXERCISE IN THE DISPOSITION OF DIETARY CALORIES: REGULATION OF SERUM LIPOPROTEIN AND CHOLESTEROL LEVELS IN HUMAN SUBJECTS. New England J. Med. *253*:349-55, Sept. 1, 1955.

Experiments with human subjects demonstrated that doubling the caloric supply of young men did not increase the serum lipoproteins and cholesterol levels as

long as the surplus energy was expended as heat and muscular energy. Accretion of this excess energy as adipose tissue caused the serum lipid levels to increase in two of three subjects. These experimental findings are related to the development of obesity, increased serum lipid levels, and atherosclerosis by American men. It is proposed that positive caloric balance over a long period elevates the serum lipid levels and contributes to atherogenesis.

Mayer, Jean; Hagman, Norma C.; Marshall, Norman B.; and Stoops, Anne Jones (Dept. of Nutrition, Harvard Sch. of Pub. Health, and Dept. of Physiol., Harvard Med. Sch., Boston, Mass.): FAT METABOLISM IN THREE FORMS OF OBESITY. V. HEPATIC LIPOGENESIS IN VITRO. Am. J. Physiol. *181*:501-03, June 1955.

Liver slices from fed and fasted animals with genetic, goldthioglucose and hypothalamic obesity and from appropriate controls were incubated with C^{14}-carbonyl-labeled acetate, and resultant C^{14} incorporation into fat was determined. Liver slices from all three forms of fed obese animals exhibited greater lipogenesis than their controls when results were expressed both per liver and per gram of fat-free tissue. Fasting decreases rates of fat synthesis in the liver of all forms of animals. However, although hepatic lipogenesis rates in goldthioglucose and hypothalamic obese animals were depressed by fasting to the same low values as observed in their nonobese controls, the rates in genetically obese mice, though depressed, remain twice as high as that observed in their controls. These results support the concept of two types of obesity: (a) metabolic, in which increased hepatic lipogenesis occurs regardless of food intake, and (b) regulatory, in which increased hepatic lipogenesis occurs only with increased food intake, which itself reflects an abnormal regulation or control of food intake.

Miley, John F.; and Brodsky, William A. (Dept. of Pediat. and the Inst. for Med. Res., Univ. of Louisville Sch. of Med., Louisville, Ky.): CONTRIBUTIONS OF URINARY AND INSENSIBLE WATER LOSSES TO THE DEHYDRATION OF METABOLIC ACIDOSIS. Am. J. Physiol. *181*:625-29, June 1955.

Dogs deprived of water for twenty hours and under Nembutal anesthesia were rendered acidotic by intracardiac infusion of 0.6 N hydrocholoric acid. During preliminary periods, values of arterial *pH and* CO_2 content were within normal limits. Rate of insensible weight loss was at a mean level of 0.30 gm./min./m.^{2}, that of urine flow 0.59 ml./min./m.^{2} After induction of acidosis, *pH* and CO_2 content diminished to values as low as 6.99 and 6.8 mm./1. respectively. The rate of insensible weight loss increased, in a widely fluctuating manner, to a mean value of 0.63 gm./min.—twice that of the preliminary rate. The maximum rate of insensible weight loss attained was as high as 2.38 gm./min. Urine flow showed a tendency to decline during the development of acidosis. The insensible weight loss, presumably of ventilatory origin, accounts for over twice the amount of weight loss, as does the renal excretion of H_2O under conditions of acute metabolic acidosis.

The assumption that approximation of insensible water loss to insensible weight loss occurred under these experimental conditions was justified. The effect of concomitant osmotic diuresis and of rate of development of acidosis on insensible weight loss was also demonstrated.

Nath, M. C.; and Bhattathiry, E. P. M. (Dept. of Biochem., Univ. of Nagpur, India): PREVENTION OF ALLOXAN DIABETES BY A CONDENSATION PRODUCT OF GLUCOSE AND ACETOACETATE. II. Metabolism 5:11-17, January 1956.

This report suggests that when the sodium salt of the condensation product of glucose and acetoacetate is injected intravenously in rabbits, endiol glucose is liberated and, in turn, combines with alloxan, forming alloxanic acid, a nondiabetic compound. Supportive evidence of this reaction is given.

Nath, M. C.; and Sahu, V. K. (Dept. of Biochem., Univ. of Nagpur, India): PREVENTION OF ALLOXAN DIABETES BY A CONDENSATION PRODUCT OF GLUCOSE AND ACETOACETATE. I. Metabolism 5:3-10, January 1956.

Glucose, immediately followed by acetoacetate, is reported to prevent alloxan diabetes in rats when injected intraperitoneally 45 minutes before the injection of alloxan. A condensation product of glucose and acetoacetate, 2-tetra-hydroxy-butyl-5-methyl-4-carbethoxy furan, similarly administered, completely prevented alloxan diabetes.

Nath, M. C.; Sahu, V. K.; and Behki, R. M. (Dept. of Biochem., Univ. of Nagpur, India): PREVENTION OF DEHYDROASCORBIC ACID DIABETES BY THE SALT OF THE CONDENSATION PRODUCT OF GLUCOSE AND ACETOACETATE. Metabolism 5:18-21, January 1956.

When the sodium salt of the condensation product of glucose and ethyl acetoacetate is injected prior to dehydroascorbic acid diabetes in rats, the latter's diabetogenic action in rats is said to be prevented.

Navazio, F.; and Siliprandi, N. (Inst. of Biol. Chem., Univ. of Rome, Italy): THE ACTION OF COCARBOXYLASE ON PYRUVATE UTILIZATION AND CITRATE FORMATION IN THE LIVER OF NORMAL AND DIABETIC RATS.

Enzymologia; Acta Biocatalytica *17*:225-28, Dec. 15, 1955.

The action of cocarboxylase on oxygen uptake, pyruvate utilization, and citrate formation by liver homogenates of normal and alloxan-diabetic rats is studied. Cocarboxylase enhances the pyruvate utilization and the citrate formation both in normal and in diabetic liver. Cystine is found to increase the cocarboxylase activity.

Papper, Solomon; Saxon, Lawrence; Prout, Thaddeus E.; and Alpert, Helen C. (Med. Serv. & Res. Lab., Boston V. A. Hosp.; and Dept. of Med., Boston Univ. Sch. of Med. and Tufts Univ. Sch. of Med., Boston, Mass.): THE EFFECT OF CORTISONE ON THE FRUCTOSE AND GLUCOSE TOLERANCE TESTS OF NORMAL MEN. J. Lab. & Clin. Med. *48*:13-19, July 1956.

The effects of a single oral dose of 200 mg. of cortisone acetate upon intravenous fructose and glucose tolerance tests were studied in ten normal subjects. Cortisone resulted in impaired glucose tolerance but did not affect fructose tolerance. It is suggested that cortisone acts in the glycolytic cycle prior to the breakdown of the glucose into three carbon fragments.

Parks, R. E., Jr.; Adler, Julius; and Copenhaver, J. H., Jr. (Dept. of Biochem. and the Inst. for Enzyme Res., Univ. of Wisconsin, Madison, Wis.): THE EFFICIENCY OF OXIDATIVE PHOSPHORYLATION IN MITOCHONDRIA FROM DIABETIC RATS. J. Biol. Chem. *214*:693-98, June 1955.

P:O ratios for several substrates were compared for normal and alloxan-diabetic rat liver mitochondria. With "short term" diabetic rats (6 to 10 days after alloxan), no consistent alterations in P:O ratios were observed, although the average ratio was lower than that of the control rats. The liver mitochondria from an occasional animal displayed a marked lowering of the P:O ratio. This was considered to be possibly the result, not of insulin deficiency, but of the irregularly occurring mild hepatotoxic action of alloxan. In alloxan diabetes of long standing (3 weeks to 6 months), no alteration in the efficiency of oxidative phosphorylation of liver mitochondria was detected. Addition of insulin in vitro did not significantly affect the P:O ratios of normal or diabetic rat liver mitochondria.

Perkoff, Gerald T.; and Tyler, Frank H. (Univ. of Utah Coll. of Med., Salt Lake City, Utah): RENAL GLYCOSURIA IN PREGNANT DIABETIC PATIENTS. A.M.A. Arch. Int. Med. *97*:758-61, June 1956.

Renal glycosuria was clinically demonstrated in five of ten pregnant diabetic patients and was probably present in three others. Prior to its recognition, the presence of renal glycosuria led to severe hypoglycemic symptoms and subsequently contributed to the occurrence of ketosis in three patients. The frequency of occurrence and importance of recognition of renal glycosuria in pregnant diabetic patients are emphasized.

RayMahasaya, D. (Dept. of Clin. Chem., Univ. of Edinburgh, Scotland): OBSERVATIONS ON THE ADMINISTRATION OF DEHYDROASCORBIC ACID IN DIABETOGENIC DOSES TO ALBINO RATS. Quart. J. Exper. Physiol. *41*:275-89, July 1956.

Fifteen minutes after the intravenous injection of 0.9 mg. of dehydroascorbic acid per kilogram of body weight in albino rats, the concentration of total ascorbic acid rose about 50-fold in the kidneys, 13-fold in the liver, and 8-fold in the pancreas. Initial marked depletion of adrenal ascorbic acid was followed by a significant increase in adrenal weight. The dehydroascorbic acid was rapidly reduced on entering the tissues. The above course of events was observed again following similar treatment on the second and third days, at which time hyperglycemia, anorexia, dehydration, and some mortality occurred.

The effects of the dehydroascorbic acid injection are interpreted by the author as resulting from stress, with adrenal hypersecretion entailing hyperglycemia and, possibly, damage to the beta cells. (Abstractors Comment: No figures for blood sugar levels and no beta-cell histology findings were included in this publication.)

Recant, Lillian (Depts. of Med. and Preventive Med., Washington Univ. Sch. of Med. and the Barnes Hosp., St. Louis, Mo.): RECENT DEVELOPMENTS IN THE FIELD OF GLYCOGEN METABOLISM AND THE DISEASES OF GLYCOGEN STORAGE. Am. J. Med. *19*:610-19, October 1955.

The enzyme systems and reactions involved in normal glycogen synthesis and degradation are reviewed in detail. This elucidation of the enzymatic steps involved in the synthesis and degradation of glycogen not only has provided an understanding of glycogen metabolism in the normal individual but has permitted an evaluation of glycogen storage diseases. Based on the clinical, biochemical, and pathological data described, these diseases have been classified into four types. Fundamental distinctions among these diseases have been demonstrated to reside in a variety of enzymatic defects in glycogen metabolism, resulting in increased tissue glycogen concentration in all cases and in abnormal glycogen structure in some.

Renold, Albert E.; and Thorn, George W. (Harvard Med. Sch., Boston, Mass.): CLINICAL USEFULNESS OF FRUCTOSE. Am. J. Med. *19*:163-68, August 1955.

The recent advances in the understanding of the metabolism of fructose are briefly summarized. The metabolism of fructose has been shown to differ from that of glucose in the following respects: The almost exclusive utilization of fructose by liver, the presence of separate enzymes for its disposal, the rate of its uptake by hepatic tissue, and the lack of any significant dependence of this rate on the presence of insulin. The abundant literature which has accumulated over the past fifty years concerning its clinical usefulness yields no conclusive answer. A fresh appraisal of the potential clinical usefulness and dangers of fructose in the light of the new knowledge concerning its physiological properties is presented.

Ricketts, Henry T. (Chicago, Ill.): THE PROBLEM OF DEGENERATIVE DISEASE IN DIABETES. Am. J. Med. *19*: 933-45, December 1955.

The nature of degenerative vascular disease and the significance of its prevalence in diabetes are discussed. The characteristics of atherosclerosis, Kimmelstiel-Wilson lesions, and diabetic retinopathy are reviewed, and the factors affecting the occurrence of vascular lesions in diabetes are critically considered. From a consideration of the available evidence, the following conclusions are reached:

Diabetes, or some factor related to it, markedly hastens the onset and increases the frequency and severity of arterial and arteriolar sclerosis. In addition, it gives rise to capillary lesions of the renal glomeruli and retina that belong almost exclusively to the diabetic state. Rates of death and disability from these causes are increasing as diabetic patients live longer. Diabetes increases susceptibility to atherosclerosis to a greater extent in women than in men. Although instances of vascular disease are observed in greater numbers among older patients, its incidence and severity in younger patients with long-standing diabetes are striking. Duration of diabetes seems to be the most important single factor. In respect to the roles played by severity and control, the best evidence indicates that the highest frequency of advanced lesions occurs in severely diabetic patients with prolonged, heavy glycosuria. However, their presence in some patients with mild, well-controlled diabetes and their absence in some cases of severe uncontrolled diabetes suggest that hereditary factors may be as important as the diabetes itself.

Although the experimental production of both glomerular and retinal lesions with cortisone and corticotropin strengthens the possibility that they have a common pathogenesis in man and raises the question of whether their clinical occurrence is related to adrenal hyperactivity, the clinical evidence on this point is contradictory. Mucopolysaccharides are increased in the blood of diabetic patients with vascular, especially renal, disease but also to some extent in those without it and may be related to the pathogenesis of retinopathy and intercapillary glomerulosclerosis. Hyperlipemia is not a prominent feature of treated diabetes. To the extent that it does exist, its association with atherosclerosis is loose and inconstant and in many cases is lacking entirely. Elevated lipid levels in intercapillary glomerulosclerosis are probably a result rather than a cause of the disease.

Ritter, Joseph A.; and Cannon, Edward J. (Pediat. Dept., Graduate Hosp., Graduate Sch. of Med., Univ. of Pennsylvania, and Wills Eye Hosp., Philadelphia, Pa.): GALACTOSEMIA WITH CATARACTS: REPORT OF A CASE, WITH NOTES ON PHYSIOPATHOLOGY. New England J. Med. *252*:747-52, May 5, 1955.

A case of galactosemia with cataracts in a six-and-a-half-year-old girl is reported. Melituria in early infancy and childhood suggests the possibility of galactosemia, and its identity should be confirmed by appropriate tests, including paper chromatography. The physiopathological aberrations may be due to direct toxic action by galactose on the cells or, more probably, to interference with availability of glucose for proper cell metabolism. The normal metabolism of galactose is not clear. Available knowledge indicates the fault in galactosemia to be in the conversion of galactose-1-phosphate to glucose-1-phosphate.

Robinson, Paul F.; and Wilber, Charles G. (Chemical Corps Med. Labs., Army Chem. Center, Md.): ATROPINE AND GLUCOSE METABOLISM IN GOATS. Am. J. Physiol. *181*:481-83, June 1955.

Study of eleven goats revealed a fasting blood glucose of approximately 80 mg. to 100 mg. per 100 ml. No significant reduction occurred in the six goats fasted for sixteen days.

The glucose tolerance curve for seven apparently healthy goats was determined after the intravenous administration of a test solution of 50 cc. of 50 per cent glucose. Two hours after the test solution of glucose was injected, the blood level of sugar had dropped from a high of 196 mg./100 ml. at 15 minutes to the preinjection level.

After sixteen days of fasting, the mean glucose tolerance curve of the goats rose to over 140 per cent of that of the controls in 15 minutes; even after three hours, the blood glucose values were 130 per cent of that of the controls. Similarly, in atropinized goats,

mean blood glucose values rose to over 200 per cent of that of the controls and remained at over 160 per cent at the end of three hours. The exact mechanism of the hyperglycemia is not clear, but it may be related to a direct action of the atropine on the sympathetic nervous system much like the action of epinephrine.

Shreeve, Walton W.; Baker, Nome; Miller, Max; Shipley, Reginald A.; Incefy, Genevieve E.; and Craig, James W. (Radioisotope Unit, V. A. Hosp., and Depts. of Biochem. and Med., Sch. of Med., Western Reserve Univ. and Lakeside Hosp., Cleveland, O.): C^{14} STUDIES IN CARBOHYDRATE METABOLISM. II. The OXIDATION OF GLUCOSE IN DIABETIC HUMAN SUBJECTS. Metabolism 5:22-34, January 1956.

Three hyperglycemic diabetics without ketosis had values for the percentage of expired CO_2 derived from glucose similar to those of the nondiabetic group. Two similar patients, along with three diabetics with ketosis, had values below those of the normal group.

The body pool in which glucose was distributed was 24, 26, and 30 per cent, respectively, of body weight in first normal, then stable, and finally labile diabetic subjects.

Shull, Kenneth H.; and Mayer, Jean (Dept. of Biol. Chem., Harvard Med. Sch.; Dept. of Nutrition, Harvard Sch. of Public Health, Boston, Mass.): THE TURNOVER OF LIVER GLYCOGEN IN OBESE HYPERGLYCEMIC MICE. J. Biol. Chem. *218*:885-96, February 1956.

The levels of liver glycogen per gram of liver were found to be similar in the obese hyperglycemic mice and their nonobese controls, but the former group had more than twice as much total glycogen. The greater total glycogen was attributed to the greater liver mass of the obese hyperglycemic mice. Mice made obese by gold thioglucose, with livers comparable in size to those of the obese hyperglycemic mice, also showed greater total glycogen levels. The levels of glycogen in representative skeletal muscles were significantly higher in the obese hyperglycemic mice than in their nonobese controls. The turnover of liver glycogen, as measured by the incorporation of uniformly labeled glucose-C^{14}, was found to be approximately six times as great per total glycogen and three times as great per gram of liver and per milligram of glycogen in the obese hyperglycemic mice as in their controls.

The metabolic significance of the data in respect to the diabetes of obese mice as contrasted to diabetes due primarily to a lack of insulin is discussed.

Slayton, Robert E.; Burrows, Ruth E.; and Marble, Alexander (Elliott P. Joslin Camp, Charlton, Mass.; Joslin Clin., Baker Clin. Res. Lab., New England Deaconess Hosp., Boston, Mass.): LENTE INSULIN IN THE TREATMENT OF DIABETES. New England J. Med. *253*:722-25, Oct. 27, 1955.

Special studies and general clinical experience with Lente insulin are reported. Lente insulin has a prolonged hypoglycemic effect, with a duration of action of approximately twenty-four hours. Its action closely resembles that of isophane (NPH)) insulin, and the two types may, in general, be used interchangeably. Crystalline insulin may be given in a single injection with Lente insulin just as with NPH insulin, with preservation of most of the rapid action of the unmodified type. This procedure is practicable and effective from a clinical standpoint. A few patients, particularly children, may complain of discomfort at the site of injection that is greater than that with other types of insulin. This is presumably due to a difference in the type of preservative used in the preparation of the insulins for the market. Allergy to Lente insulin does occur, but experience to date suggests that it is less frequent than that to other varieties.

Wosilait, Walter D.; and Sutherland, Earl W. (Dept. of Pharmacol., Sch. of Med., Western Reserve Univ., Cleveland, Ohio): THE RELATIONSHIP OF EPINEPHRINE AND GLUCAGON TO LIVER PHOSPHORYLASE. II. ENZYMATIC INACTIVATION OF LIVER PHOSPHORYLASE. J. Biol. Chem. *218*:469-81, January 1956.

This paper deals with the purification, properties, and mode of action of the phosphorylase-inactivating enzyme from dog liver. It was found that the inactivating enzyme catalyzed the conversion of liver phosphorylase to an inactive form, the activity of which was not restored by adenosine-5-phosphate. Products of the enzymatic inactivation were inactive liver phosphorylase and inorganic phosphate. Inactive liver phosphorylase sedimented at the same rate as the active form. The inactivating enzyme exhibited phosphatase action when incubated with liver phosphorylase and slight phosphatase activity was noted on incubation with phosvitin and α-casein. No phosphatase activity was noted, however, on incubation with a number of simple organic phosphate esters.

Zatzkin, Herbert R. (Meadow Brook Hosp., Hempstead, N. Y.): HEMOCHROMATOSIS WITH DIABETES, ASSOCIATED WITH CYSTITIS EMPHYSEMATOSA. Radiology *66*: 744-46, May 1956.

The author reports the finding of cystitis emphysematosa in a patient with hemochromatosis and diabetes. Diabetes was felt to favor the development of the condition.

ORGANIZATION SECTION

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Fifth Postgraduate Course in Diabetes and Basic Metabolic Problems

Columbus, Ohio, Jan. 30—Feb. 1, 1957

The American Diabetes Association will offer its Fifth Postgraduate Course in Diabetes and Basic Metabolic Problems at The Ohio State University Health Center, Columbus, Ohio, on Jan. 30-31 and Feb. 1, 1957. All lectures will be held in the Conference Theater of Ohio Union at the University.

The Director of the Course, George J. Hamwi, M.D., is Associate Professor of Medicine and Head of the Division of Endocrinology and Metabolism, The Ohio State University College of Medicine; Head, Section of Endocrinology and Metabolism, University Hospital, Columbus, Ohio. Thomas P. Sharkey, M.D., Associate Director, is Assistant Clinical Professor of Medicine, The Ohio State University College of Medicine; Consultant in Internal Medicine and Pathology, Miami Valley Hospital, Dayton, Ohio.

The Course, which is open to members of the medical profession, was developed by the Committee on Professional Education of the American Diabetes Association, under the Chairmanship of Garfield G. Duncan, M.D. It is offered in cooperation with The Ohio State University Health Center.

A Social Hour and Banquet will be held on Wednesday evening, January 30. The Social Hour is by individual subscription; registrants and faculty members are guests of the American Diabetes Association at the Banquet. Dr. Russell B. Roth of Erie, Pennsylvania, will give a humorous address entitled "Public Relations and the Physician" at the Banquet, and the internationally known Ohio State University Symphonic Choir will also entertain. Another Social Hour will be held on Thursday, January 31, at 6:30 p.m., to which all registrants,

faculty members, and their wives are invited as guests of The Life Insurance Companies of Columbus.

FEES: $40 for the three-day Course for members of the American Diabetes Association; $75 for nonmembers. The full fee is payable at the time of filing application for the Course and will be returnable by the Association to any registrant who submits his withdrawal in writing not later than January 15.

Fellows and residents engaged in full-time study in medicine and allied sciences in schools and hospitals in the metropolitan area of Columbus may attend the scientific sessions at a nominal fee of $10; interns may attend without charge. Fellows, residents and interns should register by January 15. Medical students in the metropolitan area may register without charge after January 15 if space permits.

REGISTRATION: An application form is attached to the preliminary program which has been mailed to members and subscribers to the Journal. It should be filled out and mailed to the National Office of the American Diabetes Association, together with the fee, as soon as possible. Applications will be accepted in the order received and registrations will be officially confirmed.

HOTEL ACCOMMODATIONS: The Deshler Hilton will serve as the headquarters hotel. Reservation cards will be sent to registrants with their matriculation card confirming acceptance for the Course.

POSTGRADUATE CREDIT: The American Academy of General Practice will give 22 hours Postgraduate Credit for the Course.

THE FOLLOWING TOPICS AND DISCUSSIONS (SUBJECT TO CHANGE) WILL BE COVERED DURING THE 3-DAY COURSE.

WEDNESDAY, JANUARY 30

PATHOPHYSIOLOGY OF DIABETES MELLITUS: Chairman, Frederick W. Williams

8:00 Registration
9:30 Basic Metabolic Concepts—Rachmiel Levine
10:20 Intermission
10:30 The Physiological Actions of Insulin—William C. Stadie
11:00 Factors Modifying Insulin Production and/or Utilization (a) Endocrine (b) Enzymatic—Charles H. Best
11:30 Clinical Diabetes Mellitus—Stefan S. Fajans
12:00 to 2:00 Luncheon Panel Discussion (by subscription): Moderator, Henry T. Ricketts
Panel Discussion—"Pathophysiology of Diabetes Mellitus." Participants: Rachmiel Levine, William C. Stadie, Charles H. Best, Stefan S. Fajans

DIAGNOSIS OF DIABETES MELLITUS: Chairman, John A. Reed

2:00 Laboratory Diagnosis of Diabetes Mellitus with Emphasis on Borderline Cases—Cecil Striker
2:30 Nonglucose Reducing Agents in Urine and Nondiabetic Melliturias—Alexander Marble
3:00 The Organization and Operation of a Teaching Program for the Diabetic Patient—Blair Holcomb
3:30 Intermission
3:45 Clinical Endocrine Problems Associated with Hyperglycemia—E. Perry McCullagh
4:15 Questions and Answers Period

THURSDAY, JANUARY 31

CLINICAL MANAGEMENT OF DIABETES MELLITUS: Chairman, Franklin B. Peck, Sr.

9:00 The Clinical Classification of Diabetes Mellitus—Joseph T. Beardwood, Jr.
9:20 Dietary Management of Diabetes Mellitus (a) Juvenile (b) Adult—Herbert Pollack
9:50 Practical Application of Available Insulins—Garfield G. Duncan
10:20 Intermission

ORAL HYPOGLYCEMIC AGENTS

10:30 History, Chemistry, Physiology and Toxicology—Rachmiel Levine
11:15 Clinical Results—Arthur R. Colwell, Sr.
12:00 to 2:00 Luncheon Panel Discussion (by subscription): Moderator, George J. Hamwi
Panel Discussion—"Oral Hypoglycemic Agents." Participants: Arthur R. Colwell, Sr., Rachmiel Levine, Robert M. Kark, Garfield G. Duncan, William R. Kirtley

OBJECTIVES OF TREATMENT IN DIABETES MELLITUS: Chairman, Henry T. Ricketts

2:10 Panel Discussion: Moderator, Joseph T. Beardwood, Jr.
Participants: Alexander Marble, Harvey C. Knowles, Jr., Randall G. Sprague, Henry B. Mulholland, Christopher J. McLoughlin, John A. Reed
3:45 Intermission

CONDITIONS COMPLICATING DIABETES MELLITUS

4:00 Fatty Livers—Charles H. Best

FRIDAY, FEBRUARY 1

CONDITIONS COMPLICATING DIABETES MELLITUS: Chairman, William H. Olmsted

9:00 Pathophysiology of Diabetic Acidosis—T. S. Danowski

9:40 Treatment of Diabetic Acidosis—Randall G. Sprague

10:20 Intermission

10:40 Management of Diabetes Mellitus during Elective and Emergency Surgery—Frederick W. Williams

11:10 Surgery in Diabetes—Roger D. Williams

11:35 Renal Complications of Diabetes Mellitus as Demonstrated by Renal Biopsies—Robert M. Kark

12:00 to 2:00 Luncheon Panel Discussion (by subscription): Moderator, E. Perry McCullagh
Panel Discussion—"Hypoglycemia."
Participants: Stefan S. Fajans, Howard F. Root, Harvey C. Knowles, Jr.

CHRONIC COMPLICATIONS OF DIABETES MELLITUS: Chairman, Henry B. Mulholland

2:00 Experimental Production of Renal and Retinal Lesions Simulating Those Seen in Diabetes Mellitus—J. M. B. Bloodworth, Jr.

2:20 Neurological Complications Associated with Diabetes Mellitus—Howard F. Root

3:00 Physiological Basis for Current Therapy of Degenerative Vascular Disease in Diabetes Mellitus—Henry T. Ricketts

3:30 Intermission

3:40 Clinical Pathological Conference—T. S. Danowski, Emmerich von Haam

4:30 Questions and Answers Period

FACULTY OF THE FIFTH POSTGRADUATE COURSE

JOSEPH T. BEARDWOOD, JR., M.D., *Professor of Metabolic Diseases, Graduate School of Medicine of the University of Pennsylvania; and Director, Metabolic Division, Graduate Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.*

CHARLES H. BEST, C.B.E., M.D., F.R.S., *Professor of Physiology; Director and Professor in the Banting and Best Department of Medical Research, University of Toronto, Toronto, Ontario, Canada.*

J. M. B. BLOODWORTH, JR., M.D., *Assistant Professor of Pathology, Ohio State University College of Medicine; Clinical Instructor, Endocrine Clinics, Ohio State University Health Center, Columbus, Ohio.*

ARTHUR R. COLWELL, SR., M.D., *Professor of Medicine and Chairman, Department of Medicine, Northwestern University Medical School, Chicago, Illinois.*

T. S. DANOWSKI, M.D., *Professor of Research Medicine, The University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.*

GARFIELD G. DUNCAN, M.D., *Clinical Professor of Medicine, Jefferson Medical College, Director of the Medical Divisions, Pennsylvania Hospital and Benjamin Franklin Clinic, Philadelphia, Pennsylvania.*

STEFAN S. FAJANS, M.D., *Associate Professor of Internal Medicine, Division of Endocrinology and Metabolism, University of Michigan Medical School, Ann Arbor, Michigan.*

GEORGE J. HAMWI, M.D., *Associate Professor of Medicine, Head, Division of Endocrinology and Metabolism, Ohio State University College of Medicine; Head, Section of Endocrinology and Metabolism, University Hospital, Columbus, Ohio.*

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ALEXANDER MARBLE, M.D., *Assistant Clinical Professor of Medicine, Harvard Medical School; Joslin Clinic and New England Deaconess Hospital, Boston, Massachusetts.*

E. PERRY McCULLAGH, M.D., *Head, Section of Endocrinology and Metabolism, Cleveland Clinic, Cleveland, Ohio.*

CHRISTOPHER J. McLOUGHLIN, M.D., *Instructor in Medicine, Emory University School of Medicine; Consultant in Diabetes, Grady and Piedmont Hospi-*

tals, Atlanta, Georgia.

HENRY B. MULHOLLAND, M.D., *Assistant Dean and Professor of Internal Medicine, University of Virginia Medical School, Charlottesville, Virginia.*

WILLIAM H. OLMSTED, M.D., *Associate Professor of Clinical Medicine (Emeritus), Washington University School of Medicine; Barnes Hospital, St. Louis, Missouri.*

FRANKLIN B. PECK, SR., M.D., *Associate Professor of Medicine, Indiana University School of Medicine; Consultant in Medicine, Indianapolis General Hospital, Indianapolis, Indiana.*

HERBERT POLLACK, M.D., *Associate Professor, Clinical Medicine, New York University Postgraduate School of Medicine; Associate Physician for Metabolic Diseases, The Mount Sinai Hospital, New York, New York.*

JOHN A. REED, M.D., *Assistant Clinical Professor of Medicine, George Washington University School of Medicine; Attending Physician, George Washington University Hospital, Washington, D. C.*

HENRY T. RICKETTS, M.D., *Professor of Medicine, University of Chicago; Attending Physician, Albert Merritt Billings Hospital, Chicago, Illinois.*

HOWARD F. ROOT, M.D., *Associate in Medicine, Harvard Medical School; Joslin Clinic and New England Deaconess Hospital, Boston, Massachusetts.*

RANDALL G. SPRAGUE, M.D., *Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota; Consulting Physician, Section of Medicine, Mayo Clinic, Rochester, Minnesota.*

WILLIAM C. STADIE, M.D., *Professor of Research Medicine, The John Herr Musser Department of Research Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.*

CECIL STRIKER, M.D., *Assistant Clinical Professor of Medicine, University of Cincinnati Medical College; Attending Physician, Cincinnati General and Jewish Hospitals, Cincinnati, Ohio.*

EMMERICH VON HAAM, M.D., *Professor and Chairman, Department of Pathology, Ohio State University College of Medicine and Ohio State University Health Center, Columbus, Ohio.*

ROGER D. WILLIAMS, M.D., *Assistant Professor of Surgery, Ohio State University College of Medicine; Attending Staff, University Hospital, Columbus, Ohio.*

FREDERICK W. WILLIAMS, M.D., *Associate Clinical Professor of Medicine, New York Medical College; Morrisania City Hospital, New York, New York.*

SEVENTEENTH ANNUAL MEETING

New York City will be the site of the next Annual Meeting of the American Diabetes Association, which will be held June 1-2, 1957, prior to the Annual Session of the American Medical Association, June 3-7. The Hotel Commodore will serve as headquarters hotel and individual rooms are available for members during our Meeting, as well as during the American Medical Association Session.

An announcement of the meeting together with a hotel reservation card was sent on November 1 to all Association members, who are urged to fill out the reservation card and send it directly to the Hotel Commodore as soon as possible.

SCIENTIFIC PROGRAM

The time of the first Scientific Session has been changed from last year, and will be Saturday afternoon, June 1, instead of in the morning. The other Scientific Sessions will be held Sunday morning and afternoon, June 2. A copy of the Program will be sent to all members in advance of the Meeting, and the program will also be published in DIABETES.

Physicians and other scientists are invited by Alexander Marble, M.D., Chairman of the Committee on Scientific Programs of the American Diabetes Association, to submit abstracts, not to exceed 300 words in length, of papers which they would like to present at the Scientific Sessions. Those interested are requested to submit eleven copies of the abstracts to expedite review by the Committee. A questionnaire asking for suggestions as well as abstracts of papers to be presented was sent to all members on November 1.

A Joint Meeting will *not* be held with The Endocrine Society this year. However, we have been informed that that Society will schedule its papers on diabetes for Saturday morning, June 1, preceding our opening session that afternoon. American Diabetes Association members are invited to attend that Endocrine Society session without paying a registration fee providing they present the ADA registration badge at the session, which will be held in the Hotel New Yorker.

BOARD OF GOVERNORS 1956-57

Edgar A. Haunz, M.D., of Grand Forks, North Dakota, was elected Chairman of the Board of Governors on June 9, 1956, at the time of the Sixteenth Annual Meeting in Chicago. He succeeds Louis K. Alpert, M.D., of Washington, D.C., and by reason of this office will serve as an ex officio member of the Council of the American Diabetes Association.

Other newly-elected officers include Reed Harwood, M.D., of Boston, who was elected Vice Chairman, and Henry E. Oppenheimer, M.D., of St. Louis, who was re-elected Secretary of the Board.

The Board of Governors was established in 1954. The duties of the Governors as defined by the Council are:

1. to be the Senior Delegate to the Assembly of Delegates.
2. to assist in the formation of Affiliate Associations.
3. to encourage and coordinate activities in the field of diabetes on a state level, including professional education, patient education, public education and case finding.
4. to establish liaison between the American Diabetes Association and its Affiliate organizations, as well as State and County Medical Societies and other interested groups.
5. any other duties designated by the Council of the American Diabetes Association.

Governors play an increasingly important part in current as well as future planning of ADA activities. They serve to coordinate all activities pertaining to diabetes in their respective states. Policies and programs of the national organization are interpreted to local groups; local interests and needs are in turn reflected to the Council by the Board of Governors.

The following Governors have been appointed for the organizational year 1956-57:

State	*Governor*
Alabama	Leon S. Smelo, M.D.
Arizona	Eleanor Waskow, M.D.
Arkansas	Hal Dildy, M.D.
California	
Northern & Nevada	Leo Goodman, M.D.
Southern	Roy F. Perkins, M.D.
Colorado	W. Bernard Yegge, M.D.
Connecticut	Barnett Greenhouse, M.D.
Delaware	Lewis B. Flinn, M.D.
District of Columbia	DeWitt E. DeLawter, M.D.
Florida	Sidney Davidson, M.D.
Georgia	Christopher J. McLoughlin, M.D.
Idaho	William D. Forney, M.D.
Illinois	
Northern	Ford K. Hick, M.D.
Southern	Thomas D. Masters, M.D.
Indiana	Charles E. Test, M.D.
Iowa	Robert C. Hardin, M.D.
Kansas	Thomas J. Luellen, M.D.
Kentucky	Carlisle Morse, M.D.
Louisiana	Daniel W. Hayes, M.D.
Maine	Elton R. Blaisdell, M.D.
Maryland	Ernest C. Brown, Jr., M.D.
Massachusetts	Reed Harwood, M.D.
Michigan	Laurence F. Segar, M.D.
Minnesota	Moses Barron, M.D.
Missouri	Henry E. Oppenheimer, M.D.
Montana	John A. Layne, M.D.
Nebraska	Morris Margolin, M.D.
Nevada	See Northern California
New Hampshire	See Vermont
New Jersey	Benjamin Saslow, M.D.
New York	
Eastern	Edmund L. Shlevin, M.D.
Western	George F. Koepf, M.D.
North Carolina	Charles W. Styron, M.D.
North Dakota	Edgar A. Haunz, M.D.
Ohio	Joseph I. Goodman, M.D.
Oklahoma	Bert F. Keltz, M.D.
Oregon	Wm. Richey Miller, M.D.
Pennsylvania	
Eastern	William F. Hanisek, M.D.
Western	John A. O'Donnell, M.D.
Rhode Island	Louis I. Kramer, M.D.
South Carolina	Robert Wilson, M.D.
South Dakota	John W. Donahoe, M.D.
Tennessee	Albert S. Easley, M.D.
Texas	Edmond K. Doak, M.D.
Utah	Donald E. Smith, M.D.
Vermont &	
New Hampshire	Ellsworth L. Amidon, M.D.
Virginia	William R. Jordan, M.D.
Washington	Robert L. Reeves, M.D.
West Virginia	George P. Heffner, M.D.
Wisconsin	Elwood W. Mason, M.D.

NEW OFFICERS ELECTED TO ASSEMBLY OF DELEGATES

Henry E. Oppenheimer, M.D., of St. Louis, was elected Chairman of the Assembly of Delegates on June 9, 1956, in Chicago. He succeeds Edwin W. Gates, M.D., of Niagara Falls, New York. By reason of this office, Dr. Oppenheimer will serve as an ex officio member of the Council. Mrs. Alice P. Hoover, of Cleveland, was elected Secretary of the Assembly of Delegates at the same meeting.

Each Affiliate Association selects a Medical Delegate and a Lay Delegate (if there is a Lay Society) to the Assembly of Delegates. Members of the Board of Governors serve as Senior Delegates. The Medical Delegates, Lay Delegates and Governors comprise the membership of the Assembly of Delegates.

LILLY AWARD

As previously announced, the first Lilly Award will be made at the Seventeenth Annual Meeting of the American Diabetes Association, June 1-2, 1957. The following stipulations govern the contest for the annual award, supported by Eli Lilly and Company and consisting of $500 and a gold medal.

Purpose: To recognize demonstrated research in the field of diabetes, taking into consideration independence of thought and originality.

Eligibility: Any investigator in an appropriate field of work closely related to diabetes who is less than forty years of age on January 1 of the year in which the award is made. The research will not necessarily be judged in comparison to the work of more mature and experienced workers. The candidate should be a resident of the United States or Canada.

Nominations: Nominations for the award will be solicited from the members of the American Diabetes Association. Such nominations will be requested by repeated notices to be published in DIABETES. Names of nominees will be sent to the Chairman of the Committee on Scientific Awards and must be received before January 1 of the year of the award. The nomination should be accompanied by full information concerning the nominee's personality, training, and research work. Six copies of each item should be submitted. No member may send in more than one nomination. A list of the nominee's publications, if any, and six copies of the publication or manuscript for which the award is to be given should also accompany the nomination. At the discretion of the Committee on Scientific Awards, the award may be given for work published during the year prior to January 1 of the same year of the award. The nominee should be actively engaged at that time in the line of research for which the award is to be made.

Announcement: The name of the winner will be announced in the program of the Annual Meeting of the Association, and the award presented at that meeting. The winner, subject to the approval of the Committee on Scientific Programs, will be invited to present a paper on the subject of his work. Papers considered for the award must be submitted with the idea that they will be published in whole or in part in DIABETES if found acceptable to the Editor and/or the Editorial Board. If the Committee should decide that no outstanding work has been presented for this consideration, the award will not be made.

Award: In addition to the monetary award and the gold medal, traveling expenses will be given to make it possible for the recipient to receive his award in person at the Annual Meeting.

MEAL PLANNING PUBLICATIONS AVAILABLE

Meal Planning with Exchange Lists, a booklet prepared to help diabetics select foods for their meals, Meal Plans No. 1 through No. 9 and a revised Diabetic Diet Card for Physicians, may be obtained through the offices of the American Diabetes Association, 1 East 45th St., New York 17, N. Y.

A new price schedule for this material was effective May 31. Single copies of the booklet *Meal Planning with Exchange Lists* are available at $.15 each; 100 at $6.50; 1,000 at $50.00. The separate Meal Plans (1-9), designed for use with *Meal Planning with Exchange Lists,* may be obtained at $.05 per meal plan; 100 copies of one or an assortment at $2.00; 1,000 copies of one or an assortment at $18.00. The Diabetic Diet Card for Physicians, containing information about exchange lists and food values, is available at $.05 per card; $2.00 per 100 and $18.00 per 1,000.

Meal Plan No. 1 (carbohydrate 125 grams, protein 60 grams, fat 50 grams) contains 1200 calories.

Meal Plan No. 2 (carbohydrate 150 grams, protein 70 grams, fat 70 grams) 1500 calories.

Meal Plan No. 3 (carbohydrate 180 grams, protein 80 grams, fat 80 grams) 1800 calories.

Meal Plan No. 4 (carbohydrate 220 grams, protein 90 grams, fat 100 grams) 2200 calories.

Meal Plan No. 5 (carbohydrate 180 grams, protein 80 grams, fat 80 grams) 1800 calories.

Meal Plan No. 6 (carbohydrate 250 grams, protein 100 grams, fat 130 grams) 2600 calories.

Meal Plan No. 7 (carbohydrate 370 grams, protein 140 grams, fat 165 grams) 3500 calories.

Meal Plan No. 8 (carbohydrate 250 grams, protein 115 grams, fat 130 grams) 2600 calories.

Meal Plan No. 9 (carbohydrate 300 grams, protein 120 grams, fat 145 grams) 3000 calories.

This material was prepared by Committees of the American Diabetes Association and The American Dietetic Association in cooperation with the U. S. Public Health Service. It was formerly distributed by the Health Publications Institute of Raleigh, North Carolina.

Order forms are available on request. Copies of these publications are also available from The American Dietetic Association.

ADA IDENTIFICATION CARD

As announced in the May-June 1956 DIABETES, an identification card for diabetics, issued by the American Diabetes Association, is now available. Developed by

the Committee on Information for Diabetics and bearing the official seal of the Association, the card will fit the average pocket or purse wallet. The price is $.10 each in quantities of one through nine and $.05 each in quantities of ten or more, both prices including handling and shipping. Upon authorization of the Council, a sample card was sent to each Active Member of the Association.

A VALUABLE LIBRARY

The *Proceedings of the American Diabetes Association,* containing a great body of clinical information of practical use to every physician treating diabetes, may be purchased at a special price of $34.50 for Volumes 2, 3, 4, 6, 7, 8, 9 and 10. Volumes 1 and 5 are out of print. For those who wish to complete their series, separate volumes may be obtained at $5.00 a copy. Please direct your orders to the American Diabetes Association, Inc., 1 East 45th St., New York 17, N. Y.

The *Proceedings*, previously published annually, was discontinued in 1950 with Volume 10. The publication was superseded by DIABETES, *The Journal of the American Diabetes Association.*

GLYCOSURIA AND DIABETES

A limited number of copies of *Studies Concerning Glycosuria and Diabetes,* by Frederick M. Allen, M.D., published by the Harvard University Press in 1913, are still available without charge through the courtesy of a grant from Eli Lilly and Company.

The book describes the production of diabetes by partial pancreatectomy, the first experimental production of hydropic degeneration of pancreatic islands and other early experimentations. Requests for the book should be sent to the National Office of the American Diabetes Association.

SCIENTIFIC EXHIBITS AVAILABLE

Three scientific exhibits for display at meetings of the Clinical Societies of the Affiliate Associations and other medical organizations, are available from the American Diabetes Association. They are entitled, "Management of Diabetes Mellitus," "Vascular Complications of Diabetes," and "Diabetes Detection by the Physician," and can be obtained without cost, since shipping charges both ways will be assumed by the National Organization.

1956-57 MEDICAL STUDENT-INTERN ESSAY CONTEST

The fifth Medical Student-Intern Essay Contest, sponsored by the American Diabetes Association, is open to medical students, interns and physicians within two years after their graduation from medical school. Any subject relating to diabetes and basic metabolic problems may be selected.

An award of $250 is offered to the author or authors of the best paper reporting original work, whether laboratory investigation or clinical observation. This prize is again made possible through the kindness of the St. Louis Diabetes Association. An award of $50 will be given for the best review article or case report. Papers will be judged on the basis of value of the material and method of presentation.

Members of the American Diabetes Association and subscribers to DIABETES are requested to encourage medical students and interns to enter the contest. Entrants should submit the original and one copy of their manuscript (four additional copies would be appreciated). The manuscript should be typewritten and double-spaced, and mailed by April 15, 1957, to: Committee on Scientific Awards, American Diabetes Association, Inc., 1 East 45th St., New York 17, N. Y.

NEW MEMBERS

Active

The following were elected as of Oct. 1 and Nov. 1, 1956:

Arkansas	
Martin, Art B.	Ft. Smith
California	
Masson, John Mc.	Beverly Hills
Delaware	
Smith, Alexander	Wilmington
Florida	
Lasché, Eunice M.	Tampa
Illinois	
Colwell, John A.	Chicago
Dolehide, Robert A.	Chicago
Wildberger, Henry L.	Chicago
Michigan	
Byrnes, William W.	Kalamazoo
Rapoport, Abraham	Ann Arbor
Minnesota	
Creamer, Dick O.	Rochester
Rodenbaugh, Fredrich H.	Rochester
New York	
Baer, Richard A.	Niagara Falls
Cordasco, Edward M.	Niagara Falls
Hirshleifer, Irving	Woodmere
Leone, Casmer E.	Niagara Falls
Orr, Richard H.	New York
Stone, Irwin K.	Watertown
Thomas, Theodore F.	Utica
Pennsylvania	
Leopold, Irving H.	Philadelphia
Webster, Marie B.	Philadelphia

Rhode Island	
DeCarvalho, Asdrubal S.	East Providence
Tennessee	
Wooten, Richard L.	Memphis
Texas	
Knox, Roland F.	Wichita Falls
Leiser, Alfred E.	Houston
Virginia	
Hennigar, Gordon R.	Richmond
Washington	
Cox, Robert W.	Walla Walla
Wisconsin	
Mayer, Richard J.	Racine
Other Countries	
Puerto Rico	
Suau, Pedro A.	San Juan
Corporate	
The following was elected as of Oct. 1, 1956:	
Pennsylvania	
Smith, Kline & French Laboratories	Philadelphia

NEWS NOTES

MEMBERS PARTICIPATE IN SYMPOSIUM

A Symposium on Endocrines and Nutrition, sponsored by the Medical School of the University of Michigan in conjunction with The National Vitamin Foundation, was held October 11-12 at the University of Michigan, Ann Arbor. The following papers were presented by members of the American Diabetes Association: "Primary and Secondary Aldosteronism," by Jerome W. Conn, M.D., Ann Arbor; "Newer Concepts on the Action of Insulin," by William C. Stadie, M.D., Philadelphia; "Effects of Endocrine Glands and Stress on Fatty Acid and Ketone Metabolism," by Frank L. Engel, M.D., Durham, North Carolina; "Metabolic Effects of Aryl Sulfonylurea Compounds in Normal and Diabetic Subjects," by Stefan S. Fajans, M.D., Ann Arbor.

MEETING OF THE AMERICAN DIETETIC ASSOCIATION

The 39th Annual Meeting of The American Dietetic Association was held October 9-12 in Milwaukee, Wisconsin. During the session entitled "Diabetes and Today's Research," Henry T. Ricketts, M.D., Chicago, discussed the "Treatment of Diabetes Mellitus with Oral Sulfonamide Compounds." Alexander Marble, M.D., Boston, presented "Working with Children at the Joslin Camps," and Stefan Fajans, M.D., Ann Arbor, spoke on "An Approach to the Prediction of Diabetes Mellitus."

GRANTS BY THE NATIONAL VITAMIN FOUNDATION

The National Vitamin Foundation has announced the awarding of twelve new grants, for a total of $84,295.20, to American universities to augment the extensive program of clinical and laboratory research in the fields of vitamins and nutrition. Russell M. Wilder, Sr., M.D., Honorary Member and Past President of the American Diabetes Association, is President of The National Vitamin Foundation.

The Foundation gives grants-in-aid for research semi-annually throughout the United States and abroad. The new grants became effective July 1, 1956.

DIABETES ABSTRACTS AVAILABLE

As announced in the September-October DIABETES, a number of back issues of DIABETES ABSTRACTS are available for interested members.

Nearly all of Volumes 1-10 (1942-1951), a five-year cumulative index covering Volumes 1-5 (1942-1946), and a five-year cumulative index for Volumes 6-10 (1947-1951), may be obtained without charge from the American Diabetes Association, Inc., 1 East 45th St., New York 17, N. Y. Please note that Nos. 2 and 4 of Volume 6 of DIABETES ABSTRACTS are out of print.

PERSONALS

The following members of the American Diabetes Association will participate in The Clinical Meeting of the American Medical Association to be held in Seattle, Washington, November 27-30.

HENRY B. MULHOLLAND, M.D., Charlottesville, Virginia, will act as Moderator of a panel on "Problems of Aging" on November 28. EDWARD L. BORTZ, M.D., Philadelphia, a participant in the panel, will speak on "Modern Attitudes on Aging."

On November 28 WILLIAM J. STEENROD, JR., M.D., and ROBERT L. REEVES, M.D., Seattle, will discuss "Present Day Management of Diabetic Coma." O. CHARLES OLSON, M.D., Spokane, will present "The Treatment of Diabetes Mellitus with Oral Hypoglycemia Agents Carbutamide (BZ-55) and Orinase (U-2043)" and JOHN W. STEPHENS, M.D., Portland, Oregon, will discuss "Diabetes and Pregnancy" on November 29.

LESTER J. PALMER, M.D., Seattle, will serve as Moderator of a panel on diabetes November 30 with JOSEPH H. CRAMPTON, M.D., Seattle, BLAIR HOLCOMB, M.D., Portland, Oregon, HENRY B. MULHOLLAND, M.D., Charlottesville, Virginia, ROBERT H. WILLIAMS, M.D., Seattle, and EDWARD H. RYNEARSON, M.D.,

Rochester, Minnesota, as participants.

ROBERT H. BARNES, M.D., Seattle, will present "Weight Control" as a scientific exhibit.

BERT F. KELTZ, M.D., and KELLY M. WEST, M.D., will be officers of instruction of a postgraduate course on "Selected Problems in Internal Medicine," which has been arranged by the American College of Physicians and will be held at the University of Oklahoma School of Medicine in Oklahoma City November 26-30.

ROBERT H. WILLIAMS, M.D., Seattle, was Director of the postgraduate course on "Recent Advances in Internal Medicine" given October 22-26 at the University of Washington School of Medicine, Seattle. JOSEPH H. CRAMPTON, M.D., and WILLIAM J. STEENROD, JR., M.D., were faculty members.

ADDISON B. SCOVILLE, JR., M.D., and ALBERT WEINSTEIN, M.D., were faculty members of a postgraduate course on "Seminars in Internal Medicine," held October 8-12 at the Vanderbilt University School of Medicine in Nashville, Tennessee.

ROSEMARY MURPHY, M.D., Boston, will speak on "The Hidden Diabetic" at a meeting of the Connecticut Diabetes Association and the New Haven Medical Society in New Haven on November 7.

OBITUARIES

SAMUEL S. BERGER, M.D., died Sept. 18, 1956, in Cleveland, Ohio. Born in Kis-Dobra, Hungary, April 14, 1884, he received his M.D. degree from Western Reserve University in 1904. Interning at Mount Sinai Hospital, Cleveland, he later served as Chief of its Medical Department from 1923 to 1945, and had been consultant in charge of gastroenterology since 1947. In 1906, 1922 and 1936 he pursued postgraduate work in Berlin, Munich, Vienna, Zurich, and London.

A member of the American Diabetes Association since 1941, Dr. Berger limited his practice to internal medicine. With Dr. B. S. Kline, former pathologist of Mount Sinai, he was awarded the silver medal of the American Medical Association for an exhibit at the A.M.A. Convention of 1925.

Dr. Berger was a diplomate of the American Board of Internal Medicine, and a Fellow of the American College of Physicians, and the American College of Gastroenterology. He is survived by his widow, three children and two grandchildren.

CHARLES W. LAYNE, M.D., died Sept. 21, 1956, in Newburgh, New York. Born in Fairview, Kentucky, on Nov. 16, 1900, he received his A.B. degree in 1923 from the University of Kentucky and his medical degree from Emory University in Atlanta. From 1929 to 1930 he served at Bellevue Hospital, Fourth Medical Division, in New York. In 1931 he received the Alexander Cochran Bowen Foreign Scholarship of the Academy of Medicine of New York and studied at the Vienna Allgemeine Poliklinik until 1933. Dr. Layne served as a staff member and consultant at Craig House in Beacon, New York, from 1932 to 1952 and was also a consultant at the Harlem Valley State Hospital in Wingdale, the Matteawan State Hospital in Beacon, and St. Anthony Hospital in Warwick. A former chief of staff at St. Luke's Hospital in Newburgh, Dr. Layne was attending physician there and chief attending physician at its medical and diabetic clinic. A member of the American Diabetes Association since 1941, he was also a member of the New York Academy of Medicine, and a Fellow of the American College of Physicians. In addition to his widow, he is survived by his mother, a daughter, two brothers, and a sister.

HENRY A. RANDEL, M.D., died Aug. 19, 1955, in Fresno, California. Born in Berwick, Pennsylvania, in 1902, he attended the University of Chicago and was graduated in medicine from the Northwestern University School of Medicine in 1929. After interning at the Fresno County General Hospital, Dr. Randel entered private practice in 1930. A member of the American Diabetes Association since 1954, Dr. Randel served as Regional Director for the Council on Rural Health of the American Medical Association.

Dr. Randel, who was a member of the American College of Chest Physicians, limited his practice to internal medicine. In his honor, the library of the Fresno County Tuberculosis Hospital was named the "Dr. Henry A. Randel Memorial Library" in October 1955.

DIABETES

The Journal of the American Diabetes Association

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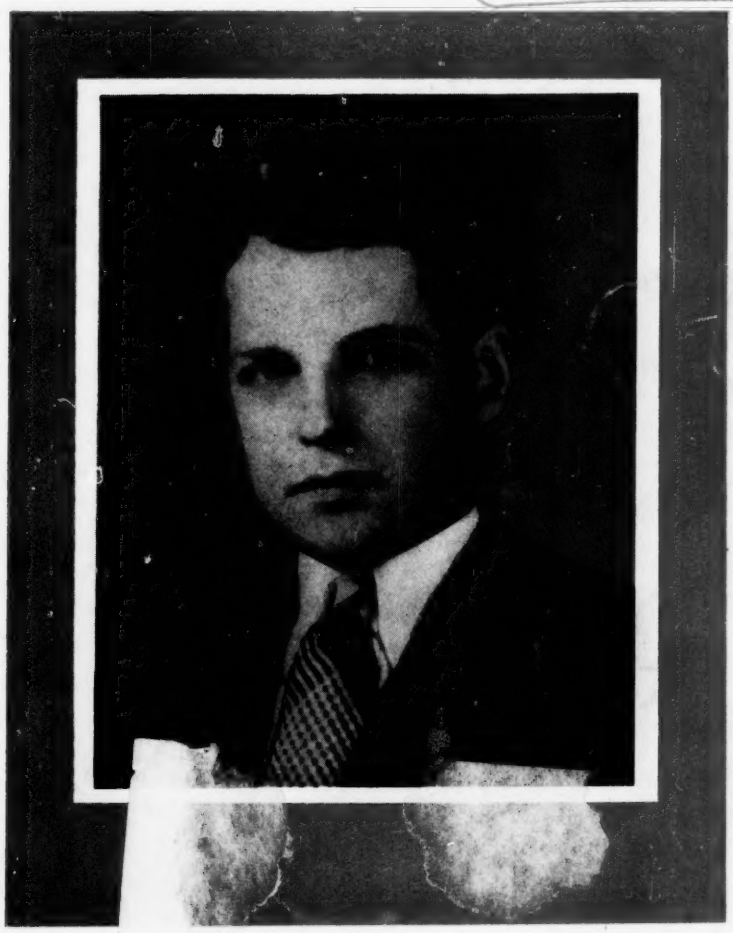

LEONARD THOMPSON

VOLUME 5, NUMBER 1 JANUARY-FEBRUARY 1956

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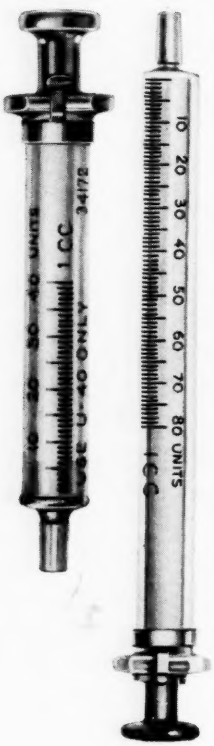

The result of careful planning and experience, Diabetic Injection Kit (No. 70) makes self-injection safer and more convenient for your patients. Designed for easy maintenance of sterile equipment, this handy kit contains STERITUBES® for carrying sterilized syringe and needles, vials for cotton and alcohol, and space for two vials of insulin. Case has been designed to accommodate the Busher Automatic Injector.

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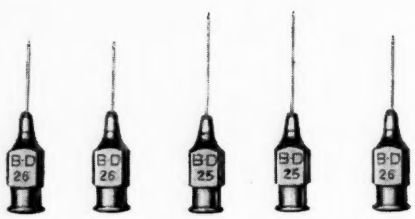

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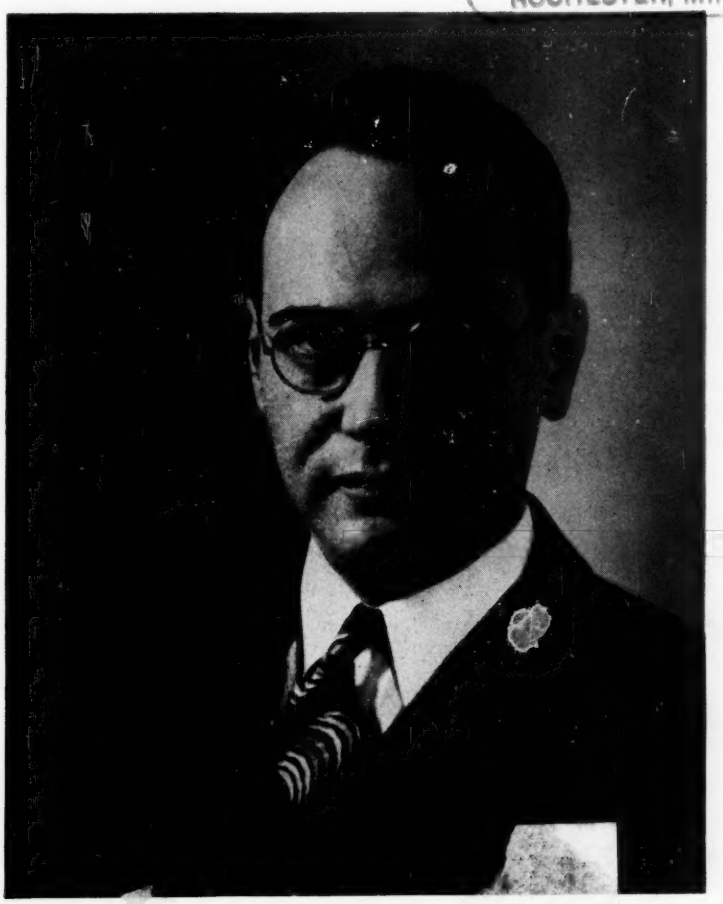

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VOLUME 5, NUMBER 2

MARCH-APRIL 1956

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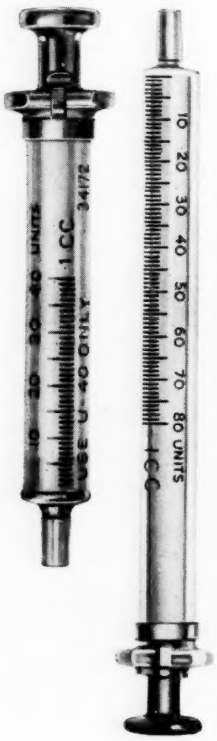

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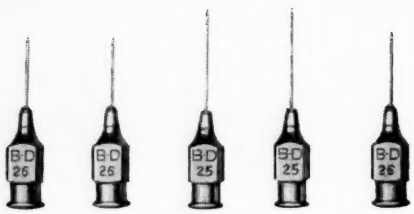

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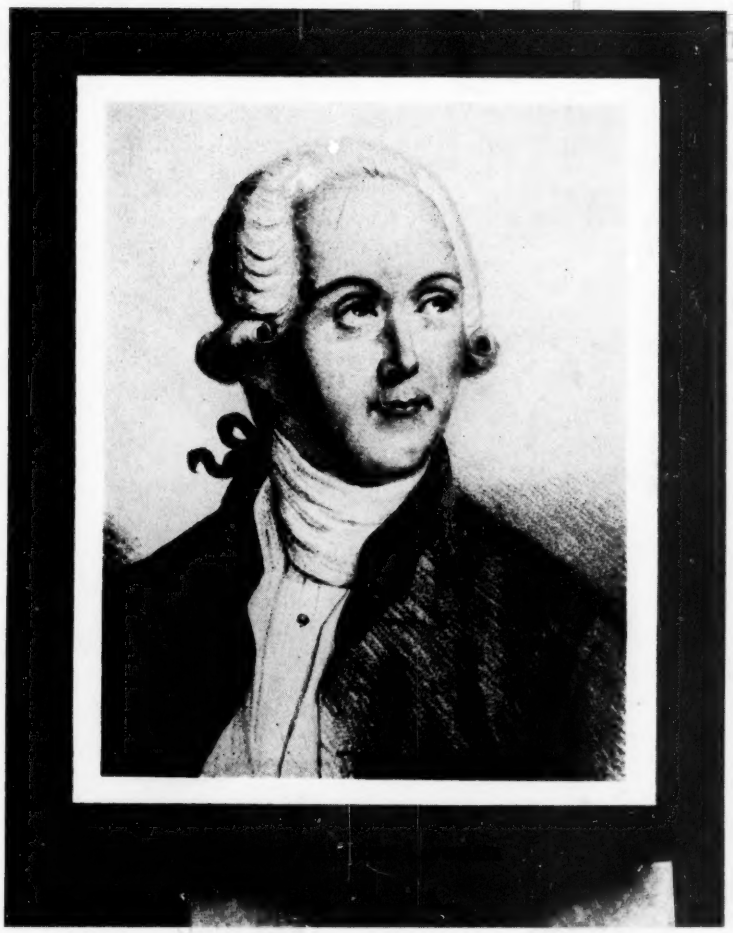

NEW YORK DIABETES ASSOCIATION SYMPOSIUM ISSUE

VOLUME 5, NUMBER 3 MAY-JUNE 1956

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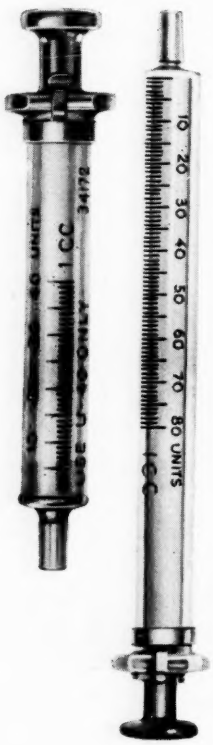

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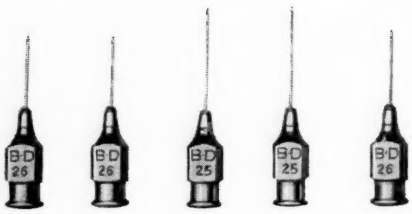

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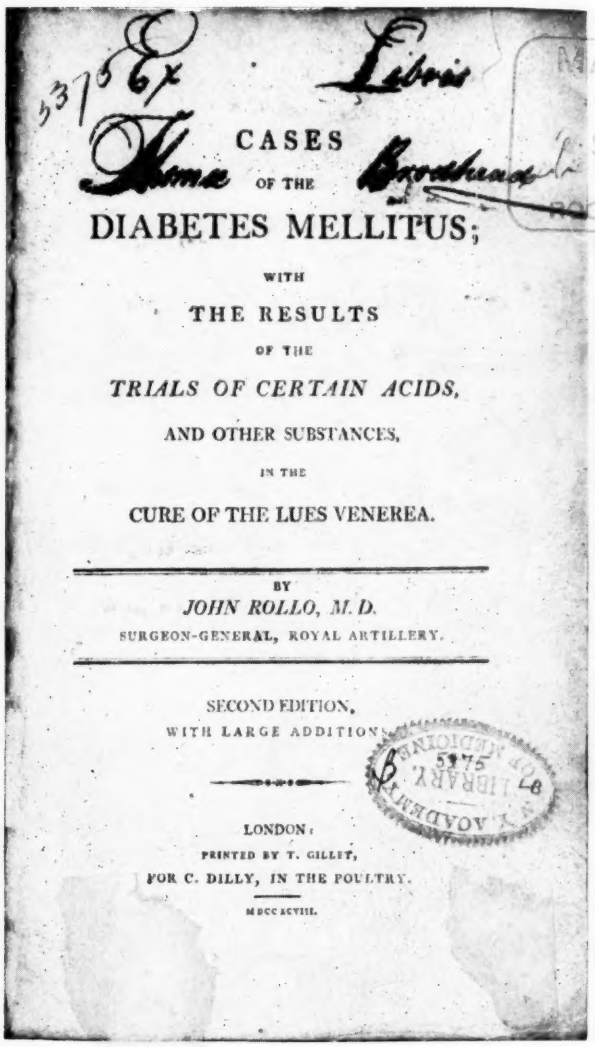
DIABETES

The Journal of the American Diabetes Association



CASES
OF THE
DIABETES MELLITUS;
WITH
THE RESULTS
OF THE
TRIALS OF CERTAIN ACIDS,
AND OTHER SUBSTANCES,
IN THE
CURE OF THE LUES VENEREA.

BY
JOHN ROLLO, M.D.
SURGEON-GENERAL, ROYAL ARTILLERY.

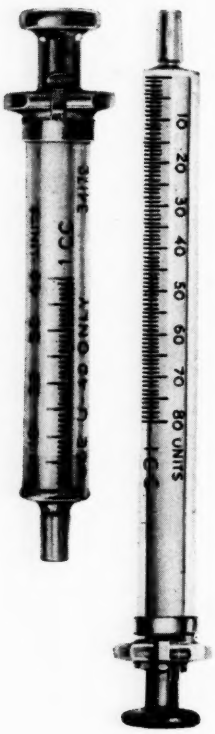
SECOND EDITION,
WITH LARGE ADDITIONS.

LONDON:
PRINTED BY T. GILLET,
FOR C. DILLY, IN THE POULTRY.
MDCCXCVIII.

VOLUME 5, NUMBER 4 JULY-AUGUST 1956

for maximum convenience and ease of self-injection

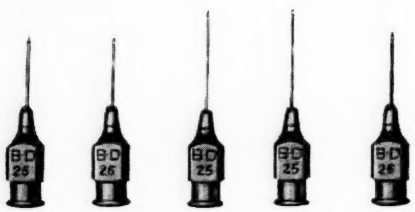
B-D DIABETIC EQUIPMENT



The result of careful planning and experience, Diabetic Injection Kit (No. 70) makes self-injection safer and more convenient for your patients. Designed for easy maintenance of sterile equipment, this handy kit contains STERITUBES® for carrying sterilized syringe and needles, vials for cotton and alcohol, and space for two vials of insulin. Case has been designed to accommodate the Busher Automatic Injector.

B-D Insulin Syringes: Individually gauged and certified for accurate dosage—different colors for different scales simplify administration of various strengths of insulin—scale markings fused on the glass for easier reading.

B-D Needles: Assure easy penetration—minimize seepage and afterpain—precision ground for greatest keenness, uniformity and safety.



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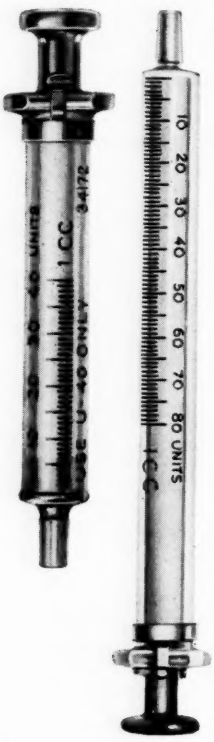

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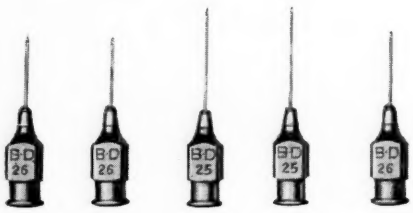

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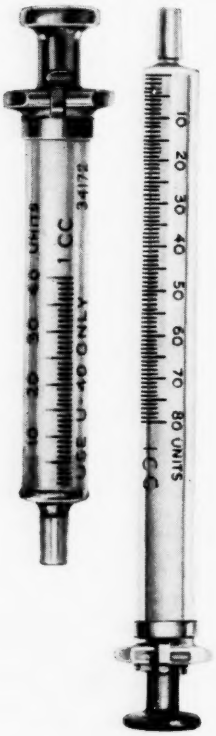

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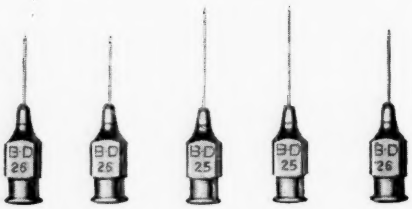

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